TASTE VERSUS CALORIES: SENSORY AND METABOLIC SIGNALS IN THE CONTROL OF FOOD INTAKE

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TASTE VERSUS CALORIES: SENSORY AND METABOLIC SIGNALS IN THE CONTROL OF FOOD INTAKE*

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THE PROBLEM: TASTE VERSUS CALORIES

In this paper we would like to discuss the role of sensory and metabolic signals in the control of food intake. The problem can be defined by perusing FIGURE 1, which presents a simplified version of a previously published schema outlining the control of intake in flow chart form (Jacobs, 1962). The initial conditions assume an animal already eating food. We shall not be concerned with the particular causes initiating the meal. Starting with the top of the FIGURE 1, then, we may ask classical question of physiologists analyzing intake regulation: What does the diet contain that can act as a signal to monitor subsequent intake? This signal can increase intake in a short-term positive feedback loop, as seen in the lower right side of the Figure, or decrease it in a negative feedback loop. The latter case we have called satiety.

The two classes of physicochemical stimuli which interest us are labeled calories and taste. Both sets of signals are initiated in specialized receptor systems and relayed to the central nervous system (CNS) by nervous and/or humoral paths.

It should be pointed out that our choice of the terms, taste and calories, is an oversimplification of the actual situation, which is at least hinted at in FIGURE 2. This diagram shows the same system, with the physicochemical stimuli expanded. What we have called calories are in fact only one of a large number of potential metabolic signals, and taste, only one of a number of potential sensory signals. The metabolic class includes all of the classical factors that physiologists have implicated in food intake. When a single factor is singled out and perhaps overemphasized, we have a "theory" of intake, as in the classical glucostatic and thermostatic hypotheses. Some would also consider a lipostatic or perhaps an "aminostatic" theory as well. Most people working in this area now accept Edward Adolph's dictum that food intake is under multiple factor control, and that some combination of all of the metabolic signals is involved. The sensory category summarizes the classes of stimuli contained in food which have been of interest to the sensory psychologist, but which, for the most part, have been ignored by the regulatory physiologist.

FIGURE 2 suggests many interesting problems, e.g. which receptor system responds to which classes of stimuli? Where are the latter located? Are they independent? For the purpose of this discussion, we can ignore these complexities. Returning to the simpler case (FIGURE 1), we can now point out that the terms,

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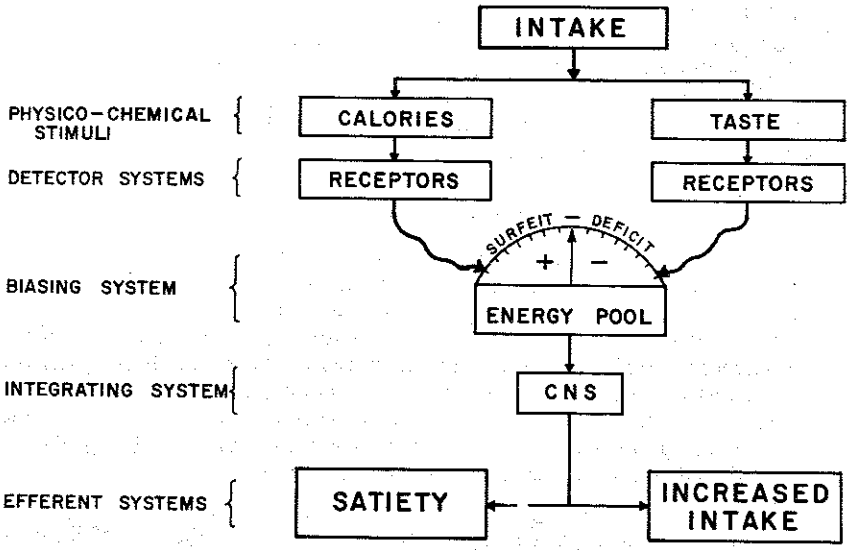

FIGURE 1. Simplified schema of taste and calories as cues in the regulation of food intake.

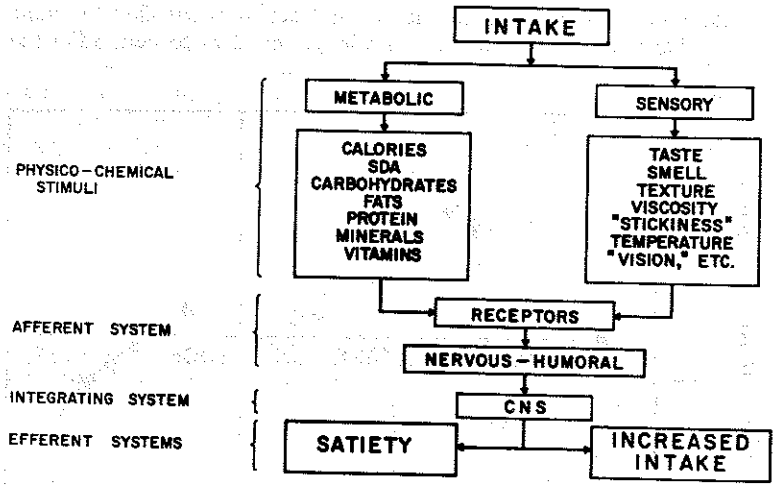

FIGURE 2. Generalized schema of sensory and metabolic feedback systems in food intake.

taste and calories, in this diagram are actually shorthand terms for a complex of factors. What we call calories, then, may actually be heat, blood glucose shifts, etc., and what we call taste may, in fact, be taste, smell, and so on. Thus, for purposes of this discussion, the term "calories" will be considered equivalent to "metabolic," and that of "taste" equivalent to "sensory."

Our task in this paper is to consider the relative importance of calories and taste in a control system of the type outlined here. I will proceed as follows: First,

I will briefly review current views on the relative importance of taste and calories in the control of food intake and present some of our reasons for questioning them. I will then outline a model which is at variance with these views, and present some of the evidence which we have gathered to evaluate it. I will take the liberty of eliminating irrelevant procedural details and of substituting typical examples for an exhaustive review of the literature.

Current View: Animals Eat for Calories

Most of the classical and current work on food intake by physiologists and nutritionists emphasizes the importance of metabolic factors. This is not to say that sensory factors have been completely ignored. There are many studies that have implicated taste and flavor in food preferences (e.g. Young, 1948; Kare, 1961; Pangborn, 1964), but little systematic consideration has been given the role of taste as part of the physiological system controlling intake. One notable exception is the work of the group under J. LeMagnen (this monograph) who has been analyzing the dual role of sensory cues as conditioned satiety signals and as unconditioned stimuli for anticipatory metabolic reflexes.

I believe that the following comments are perhaps more typical of the conclusions most of us draw in reading the animal research on the role of taste vs. calories in the control of food intake. In 1948 E. M. Scott reviewed this problem and concluded as follows, "There is only one known true hunger. This is the appetite for food as such, and, in the rat at least, it is satisfied by sufficient calories . . . There are, to the authors knowledge, no data to contradict the as-

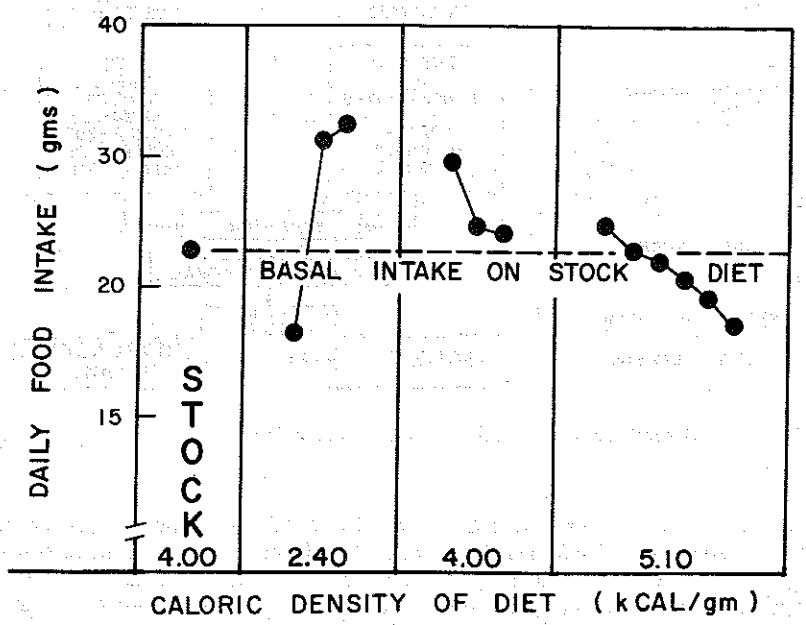

Figure 3. Effect of changes in caloric density of the diet on intake in *ad libitum*-fed rats. (N = 12). Stock diet (4.00 kcal/g), 40% cellulose diet 2.40 kcal/g), 25% fat diet (5.10 kcal/g).

sertion that normally rats eat for calories." (Scott, 1948, p. 126). This conclusion is even occasionally applied to man as well, as in Sebrell's discussion of protein intake at the Fifth International Conference of Nutrition. Commenting on failure of individuals to recognize protein deficiencies easily when they occur, he noted that "man, driven to eat by the sensation of hunger, becomes satiated when his caloric needs are met." (Sebrell, 1961, p. 393).

What kind of evidence is available for justifying such a broad conclusion? For the most part it is quite straightforward and simple and comes from classic diet dilution experiments. For example, rats will adjust food intake to its caloric density, under a wide variety of conditions, ignoring dietary additives such as cellulose, kaolin, glucose, saccharine, quinine, and assorted flavors. FIGURE 3 shows the typical results of one such study, carried out in our laboratory several years ago. Going from left to right on the Figure, we see that rats ingest about 22 g of stock diet in *ad libitum* feeding, increase intake with cellulose dilution, return to baseline on stock diet, and decrease intake with the addition of corn oil. Adolph and others have interpreted such data as suggesting that rats have a "calorie counter" (Scott & Quint, 1946; Adolph, 1947; Teitelbaum & Epstein, 1963). Epstein and Teitelbaum concluded that these adjustments are independent of taste by showing that rats continue to adjust to dilution of liquid diets when taste and smell are bypassed by feeding via a chronically implanted gastric tube (Epstein & Teitelbaum, 1962). Work on sugar solutions in our laboratory led us to identical conclusions (Jacobs, 1961 & 1962).

Thus, it would appear that rats control intake by responding to the nutrient properties of the diet and that taste and smell are dispensable. There is one obvious limit to this generalization. Work on hypothalamic hyperphagic rats shows clearly that caloric regulation of food intake depends upon an intact CNS. Ventromedial lesions produce obese, but finicky, rats, which ignore caloric density and overreact to taste. (Teitelbaum & Epstein, 1963). The brain-damaged rats would react quite differently than our normal, *ad libitum*-fed rats, as shown in FIGURE 3. They would *decrease* their intake on cellulose and *increase* it on fat.

LIMITATIONS ON CURRENT VIEWS

In summary, there is general agreement in the literature that normal rats eat for calories. Our own interest in this problem developed during a program of work on glucose appetite. Review of the literature turned up an interesting set of facts. First, the published experiments in which animals clearly showed regulation to dilution with non-nutritive bulk have been carried out under *ad libitum* feeding schedules, (e.g. McCay *et al.*, 1934; Adolph, 1947; Strominger *et al.*, 1953). Second, several studies reporting difficulties in getting adjustment to diet dilutions, or intragastric glucose loads, were carried out on hungry animals (e.g. Janowitz *et al.*, 1949; Janowitz & Grossman, 1949; Janowitz & Hollander, 1955; Smith *et al.*, 1962). LeMagnen (1963) also noted these failures of adaptation in hungry animals in his review of the literature. In the third place, many workers have shown that hunger increases the intake of sugars, which contain taste as well as calories, and saccharine, containing taste alone.

The latter effects are very striking. For example, as early as 1944, Soulairac showed that insulin-induced hunger increases the intake of 10% solutions of maltose, glucose, and sucrose in direct proportion to their sweetness (Soulairac, 1944). We later verified this, using glucose and fructose solutions (Jacobs,

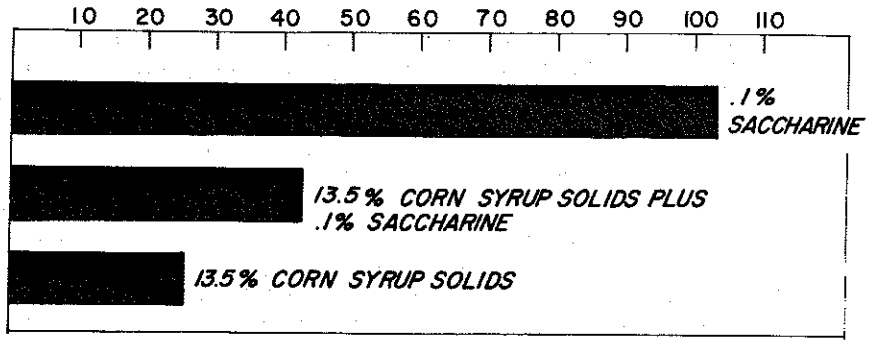

FIGURE 4. Effect of hunger (20-hour food deprivation) on the intake of nutrient and/or sweet solutions. (N = 6).

1967).* In 1954, LeMagnen, using a 30-minute drinking test, showed that food deprivation increased the intake of a non-nutrient saccharine solution *more* than it did a less sweet glucose solution (LeMagnen, 1954).

We modified LeMagnen's (1954) approach to this problem by independent variation of taste and calories. This was accomplished by the use of unsweetened corn syrup solids, a complex polysaccharide that is isocaloric with glucose, but rather than sweet, is very bland tasting. We used this substance to measure the effect of adding sweetness to calories in hungry rats. Six rats were given one-hour, single-bottle intake tests while *ad libitum*-fed. These tests were then repeated after the animals were adapted to a 20-hour food deprivation schedule. Dry food was not available during the test periods. The test solutions used were corn solids, providing calories alone, a saccharine-corn solids mixture, with sweetness and calories, and saccharine, containing sweetness alone. During the *ad libitum* period, the rats responded to calories, ignoring the sweetness added to corn solids by ingesting equal amounts of corn solids and glucose. The effects of hunger are shown in FIGURE 4, which presents the data as percentage increase in intake induced by hunger. Food deprivation significantly increased intake of all three solutions. The differences in percentage increase were also significant. Thus, in agreement with the results of LeMagnen (1954), hunger seemed to affect taste more than calories as cues for meal size.

A WORKING HYPOTHESIS AND MODEL: A DUAL SYSTEM REGULATED BY ENERGY BALANCE

The studies outlined so far suggested that the relative importance of taste and calories may be related to the state of energy balance. This possibility was offered as a tentative working hypothesis in a paper on sugar preference (Jacobs, 1962, p. 1052). This hypothesis asserted that the urge to eat for calories was limited to *ad libitum* feeding schedules, and that hunger made taste more important. As

* Correlations between sugar intake in rats and taste judgments in man (e.g. Cameron, 1947), should take into account electrophysiological rankings for the same sugar series. For example, in the series used by Soulairac (1944) and Jacobs (1967), human judgments order sweetness as fructose>sucrose>glucose>maltose. Although available electrophysiological evidence suggests that sucrose>glucose>maltose (Pfaffman & Hagstrom, 1959), and fructose>glucose (Tateda & Hidaka, 1966), there is one interesting reversal of this trend. Recent evidence shows that fructose produces *less* electrical activity at the chorda typani nerve than sucrose, when both sugars are tested at less than 1 mole (Tateda & Hikada, 1966).

applied to the problem of solution preference, this is similar to the "behavioral regulation" hypothesis used by Richter (1939) to explain the specific appetite for salt in adrenalectomized rats, to Katz's "avidity theory" (1953) to explain all specific appetites, and to LeMagnen's concept of a "primary response" in the short-term control of solution intake (LeMagnen & Pieron, 1953; LeMagnen, 1954). The three hypotheses are identical in assuming that organic need alters perceptual bias on an innate basis, so that the animal seeks out and ingests the needed food on the basis of its sensory qualities. The fact that food contains nutrients is considered coincidental.

Our own version of this type of hypothesis, schematized to include dry, complete diets as well as solutions, and general, as well as specific, hungers, is formalized in the model shown in FIGURE 5. This Figure presents a simple extension of the previous schematics (FIGURES 1 & 2), showing that physicochemical information from the diet feeds into two detector systems which can respond to signals from either taste or calories. Whether the CNS makes use of either set of signals in monitoring further intake is a function of the state of energy balance. The energy pool acts as a biasing system, assigning prority to taste when the animal is in deficit, and to calories when it is in balance or surfeit.

The model, however, appears to be in direct conflict with common sense. Common sense assumes that hungry animals are *less* discriminating about taste in their excited search for calories, and that one has time to be a gourmet only under conditions of relative surfeit. What we are saying in this diagram is that the animal eats for calories when he does not need them, and eats for taste when he needs calories. Thus, for us, the hungry animal is *more,* rather than *less,* discriminating, much like the "finicky" hypothalamic hyperphagic rat. This model, in fact, suggests a specific analogue between the normal, hungry animal, and the hypothalamic hyperphagic rat. Teitelbaum and Epstein (1963) have contrasted the lesioned preparation with normal, intact animals. This model argues that the contrast should be limited to the normal rat only under *ad libitum* feeding conditions, on the surfeit side of our diagram and that the hypothalamic hyperphagic is merely a pathological caricature of the normal animal in severe energy deficit, with the important difference that the normal animal is in energy deficit, while the obese animal is being fooled by misinformation, signaling a nonexistent deficit.

One final point about FIGURE 5: We do not visualize this as a double-throw

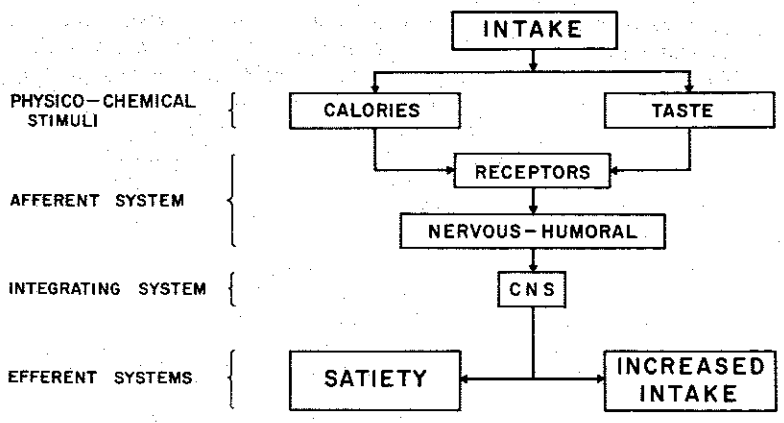

FIGURE 5. Model of the role of energy deficit in the regulation of food intake.

switching system, in which either detector system can be completely shut off. We know that *ad libitum* animals *can* respond to taste. For example, they like saccharine (Beebe-Center *et al.*, 1948). We also know that hungry animals *can* respond to calories. For example, a hungry rat can learn to turn its head for i.v. injections of glucose used as reward (Coppock & Chambers, 1954). Thus, we would say that the animal is always capable of responding to either taste or calories, and that energy balance merely changes their relative importance in monitoring intake.

Experimental Evaluation of the Model†

I would now like to describe several sets of experiments that we have carried out in an attempt to evaluate this model. Although the model was initially developed in the context of an analysis of glucose appetite (Jacobs, 1962), we have designed the experiments reported here to evaluate its applicability to food intake in general. The experiments were quite simple, independently varying taste and calories so that we could determine which cue the animal was following. We then compared the relative importance of these cues in *ad libitum* feeding or under energy deficit, or in one case, in *ad libitum*-fed neonate rats. Taste and calories were varied by manipulation of the test food presented to the animal.

Taste and Caloric Regulation in the Dog

Cellulose Dilution. First a study of taste vs. calories in the dog. Most of us consider the dog a natural gourmand, ravenously eating so rapidly that he could not possibly respond to taste. This suggests that dogs eat for calories. However, unlike the rat, clear evidence in the dog is hard to find. The classic dilution experiments of Cowgill in 1928, and Janowitz and Grossman two decades later showed sluggishness and occasionally complete failure to respond to caloric dilution. Our model would lead us to expect that their animals may have been in relative energy deficit, attending to taste more than calories. In both of these cases none of the authors noted meal time as an important variable. Presumably, each experimenter had his animal caretaker feed the dogs according to local custom. Cowgill (1928) allowed a three-hour daily meal and Janowitz and Grossman (1949) allowed 45 minutes. If these were rat experiments, nutritionists would have to classify these procedures as "spaced-feeding experiments," and psychologists would call them "food-deprivation schedules." This was a confusing situation. We decided to investigate the matter by contrasting a relative energy deficit imposed by a daily 15-minute meal with a true 24-hour *ad libitum* feeding schedule. Bringing our long experience as rat caretakers to bear on this problem, we developed a nonspillable food cup for dogs, made up of a plastic dishpan and a galvanized metal garbage can, as shown in FIGURE 6, which worked beautifully.

FIGURE 7 shows the results of diluting the diet with 25% cellulose. The raw data for three *ad libitum* dogs are plotted on the bottom of the Figure, and those for three hungry dogs are plotted on the top. These dogs were given 13 days of stock diet and then presented with 25% cellulose-diluted diet for ten more days. The *ad libitum*-fed dogs, eating about 250 g per day, showed a gradual trend to increased intake of diluted diet, presumably eating for calories. The food-deprived dogs were finicky, much like the brain-damaged rats described earlier. They

† Preliminary reports on most of this material can be found in Jacobs, 1961, 1962, 1963, 1964, 1964a, 1966, 1967, Jacobs and Sharma 1964, 1964a, and Jacobs *et al.*, 1965.

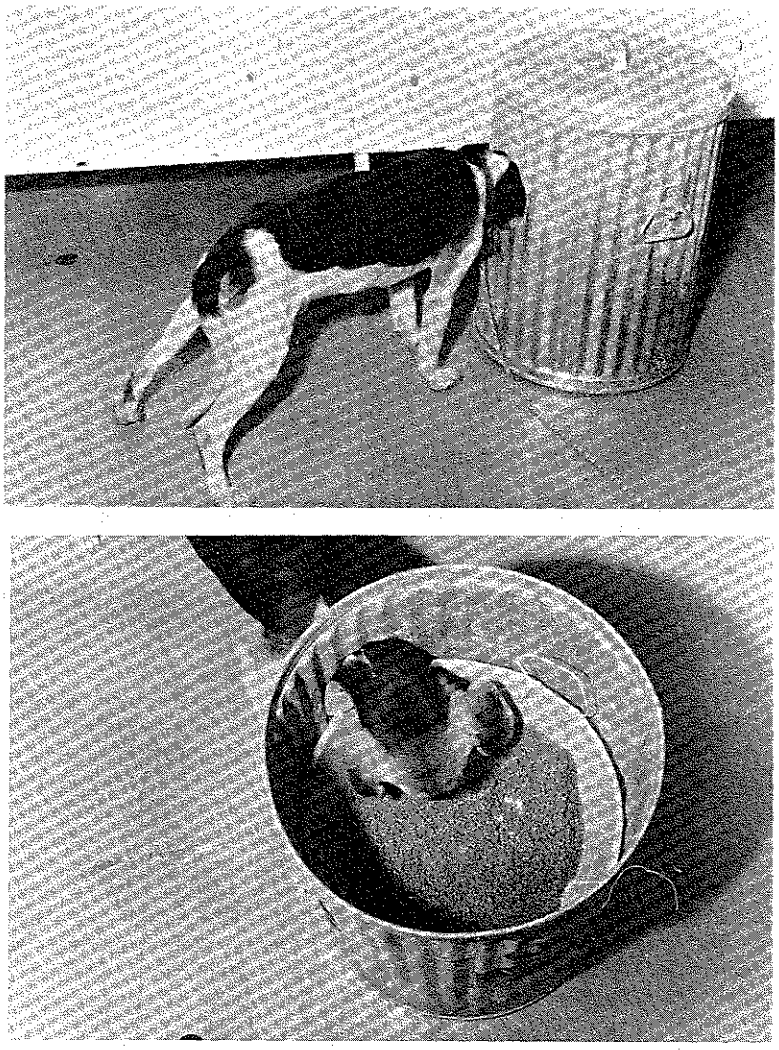

FIGURE 6. An all weather device for 24-hour *ad libitum* feeding experiments.

refused to ingest the diluted diet and showed little adaptation over the ten-day test period.

Water, Saccharine, and Quinine Additives. Our interpretation of these data is that the food-deprived dogs were ignoring calories and responding to taste. FIGURE 8 shows a more direct test of this interpretation with the same two groups of dogs. Daily intake in grams is plotted on the vertical axis, and experimental diets presented in one-day tests are plotted on the horizontal axis. In A, both groups ingest almost equal amounts of stock diet over an eight-day test. In B,

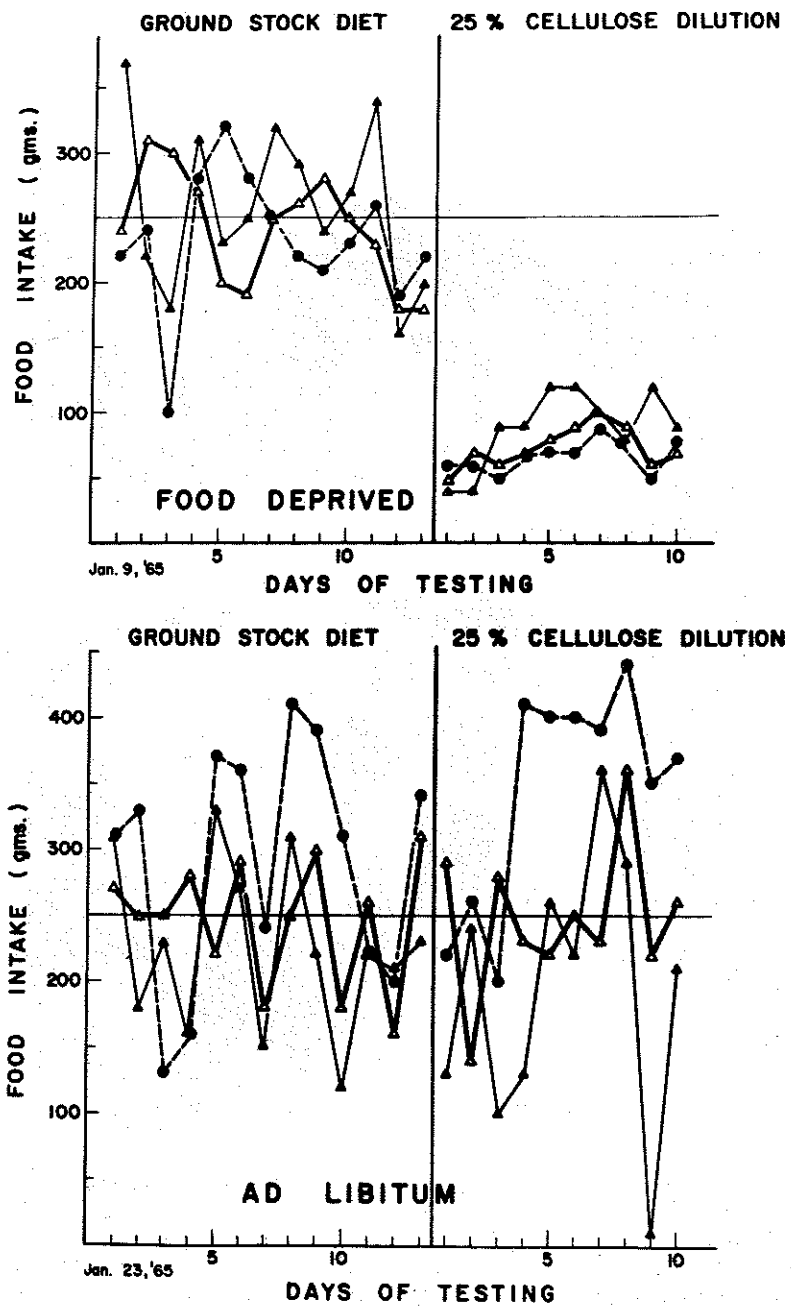

FIGURE 7. Effect of cellulose dilution on the intake of stock diet in *ad libitum* (N = 3) or food-deprived (N = 3) Beagle dogs.

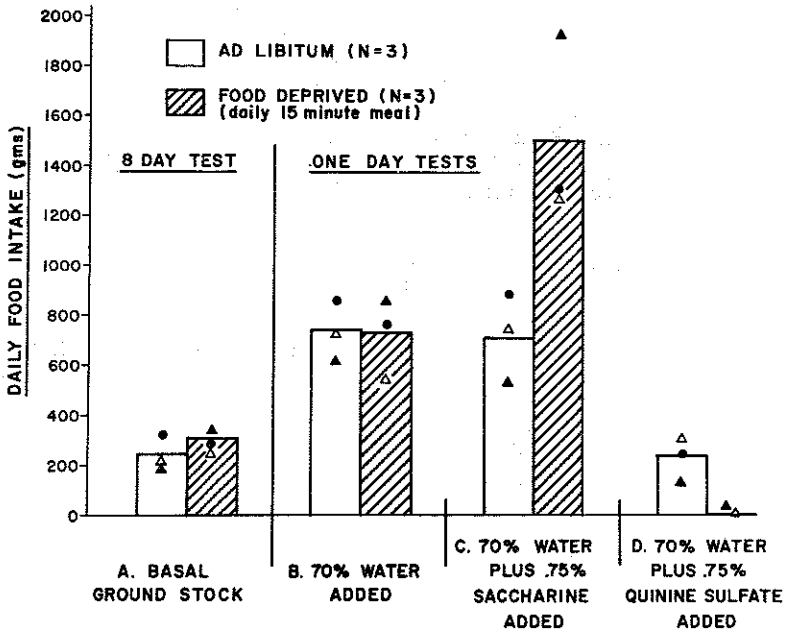

FIGURE 8. Effect of wetting diet and saccharine or quinine flavor on food intake in Beagle dogs.

diluting the diet with water increased intake equally. Perhaps both groups were eating for calories? Our model would explain the results in B by assuming that the *ad libitum* dogs increased intake in response to calories, while the hungry dogs merely found the wet diet more palatable. The results in condition C where .75% saccharine was added to the wet diet, are in agreement with this rather speculative interpretation. The *ad libitum* group ignores the saccharine additive in C, continuing to compensate for the water dilution of calories. The hungry dogs double their intake of the saccharine solution, presumably responding to its taste. In D, we tried a very bitter quinine additive. The *ad libitum* group did not like it, but merely returned to their normal intake. The hungry animals completely refused to eat the bitter food. Thus, precise control of feeding schedules shows that dogs can indeed respond to taste, apparently as a function of relative energy deficit.

Taste and Caloric Regulation in the Adult Rat

Cellulose Dilution and Fat Additives. FIGURE 9 presents further analysis of the case of cellulose dilution of stock diets, comparing 22-hour food-deprived rats with 24-hour *ad libitum*-fed animals. As expected, the *ad-libitum* animals, in A, eat for calories. They ingest about 20 g of stock diet per day, and increased intake when 40% cellulose was added. In B, the food-deprived rats decreased intake with cellulose dilution, responding like our hungry dogs, or the ventromedial-lesioned obese rats reported in the literature (Teitelbaum, 1955). In C, we added an emulsion of corn oil and water to the high cellulose mixture, which promptly *increased* intake, for the hungry rats.

It should be noted that the hungry animals failed completely in their adjustment

to caloric density. They decreased intake with a decrease in kcal/g from 4.00 to 2.40 in B, and increased intake when it increased to 2.90 in C. Our interpretation of these results is that cellulose dilution presented an unpalatable combination of taste qualities, compensated for by the palatable additive.

There is an attractive alternative hypothesis to the taste interpretation of these data, offered by Smith *et al.* (1962) in a similar experiment in which they found that hungry rats failed to adjust to dietary addition of non-nutritive bulk. It is

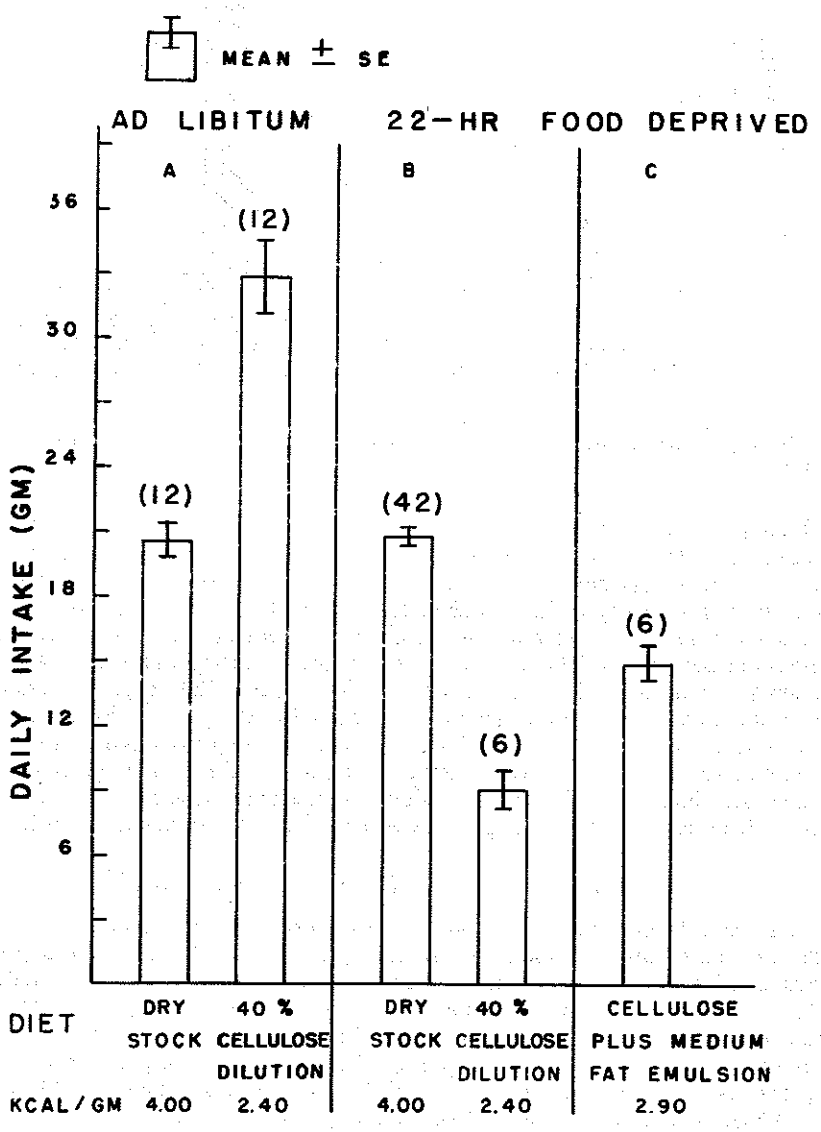

FIGURE 9. Effect of food deprivation on food intake in response to dilution of stock-diets with cellulose and corn oil. Parentheses enclose number of observations in each treatment.

to assume that bulk may be a limiting factor in the two-hour meal and that the rats merely ingested equivalent volumes of stock, low-density cellulose, or the high-density water and corn oil emulsion. Analysis of the specific gravity of the diets, and computation of the actual components ingested in these mixtures produced adequate evidence against the bulk hypothesis. For example, in FIGURE 9, the addition of the medium-fat emulsion (in C) to the 40% cellulose diet (in B) increased intake enough to provide more stock diet, more cellulose, plus the added emulsion itself; thus, it must have also provided more total bulk. Our conclusion, then, is that the hungry rats were responding to the cellulose and water-corn oil emulsion on a common basis and that this basis was taste, not volume.

Ingestion of Pure Cellulose. At this point we decided to present pure cellulose to hungry rats and to vary taste by the addition of palatable, non-nutrient additives. In anticipating a breakdown of discrimination in hungry animals, common sense might predict some ingestion of pure cellulose, at least until the rat ate enough to detect the absence of a caloric signal in the ingesta; it certainly would not predict a specific effect of changing the taste of the cellulose. Our model would lead us to expect almost no intake of cellulose, because of its taste. Further, we should be able to induce ingestion of pure cellulose by choosing palatable non-nutrient additives.

FIGURE 10 shows the results of such an experiment, carried out on 22-hour food-deprived rats. Almost no cellulose was ingested during the two-hour test

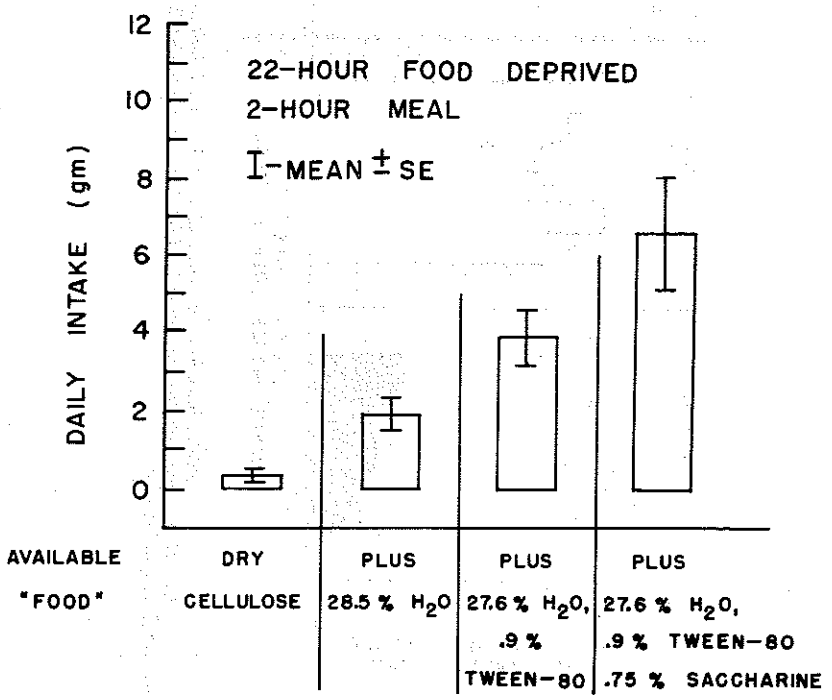

FIGURE 10. Effect of palatable, non-nutrient additives on the ingestion of pure cellulose in food-deprived rats. (N = 6).

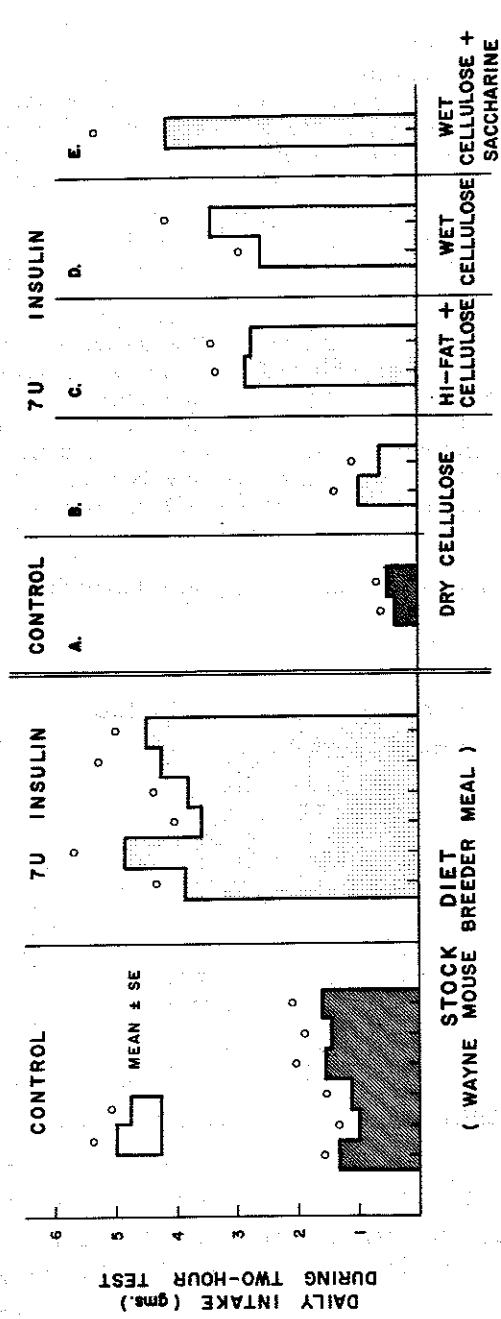

FIGURE 11. Effect of s.c. insulin injections on stock diet intake of *ad libitum*-fed rats in response to cellulose dilutions and palatable additives (N = 5). A. and B: Diets, 40% cellulose in stock; C: Diet, 25% corn oil plus 2.8% water in stock; D: Diet, 27.7% water in stock; E: Diet, 27.7% water plus .75% saccharine in stock.

period. Going from left to right, the addition of water, water plus tween-80 (Nutritional Biochemicals Corp., Cleveland, Ohio), or the latter two plus saccharine, all increased cellulose intake. Common sense might argue that two hours was too short to allow the rat to respond to the lack of a caloric cue. Thus, we repeated it with a 24-hour feeding test with identical results. The rats ate nothing in two hours and only .3 g in 24 hours; with liquid additives of the type shown in FIGURE 10, they ingested up to 15 g of the zero-calorie mixture in 24 hours.

Insulin and Cellulose Dilution. In summary, our work with cellulose dilution is in agreement with our theoretical model, suggesting that hungry animals are biased toward taste cues in regulating intake. It could be argued, however, that comparing a two-hour meal (in rats) or a 15-minute meal (in dogs) with a 24-hour baseline is complicated and open to other interpretations. Thus we decided to repeat some of our rat experiments using 24-hour *ad libitum* schedules for all animals. Hunger was induced by injections of crystaline insulin, allowing a meaningful comparison of a hungry and a satiated animal with a two-hour intake test in both cases.

FIGURE 11 presents the results of these experiments, plotting intake in a series of consecutive daily tests. The dark bars show the intake with control injections of saline. All of the light bars show intake following insulin injections. First, it is necessary to note the two sets of bars to the left of the heavy double lines, which shows the intake of stock diet. As expected, insulin hunger significantly increased the intake of stock diet. Continuing across the Figure to the right of the double line, we see first that the insulin-hungry rat, in *B*, significantly fails to increase its intake of the cellulose diluted diet as it did when stock diet was present. Our model suggests that this is a case of "finickiness." If so, palatable additives should increase the intake of the cellulose diet. This is indeed the case, for as we continue to the right from B, where the addition of corn oil, in C, wetting the diet, in D, or wetting the diet with saccharine additive, in E, we see that all significantly increased the intake of the cellulose diet. Thus, the results on hunger induced by insulin are in agreement with our cellulose dilution experiments, using hunger induced by food deprivation.

Fat Additives in Isocaloric Diets. Our interpretation of the cellulose dilution series described thus far depends upon our assumption that corn oil increases the intake of hungry rats because of its taste, and not because of its caloric value. However, whenever corn oil was added to high cellulose diet in these experiments, it increased caloric density concomitant with any taste changes it produced (see FIGURES 9 & 11). Was the change in caloric density a necessary condition for the corn oil's potentiation of intake in hungry rats?

The experiments summarized in FIGURE 12 analyze this possibility. Our procedure was to add 13.5% corn oil to dry stock, and compensate for the increase in calories by adding appropriate amounts of water until the dry stock diet and the mixture of stock plus medium fat were isocaloric at 4.00 kcal/g. Thus, any change in intake would be attributable to taste changes alone.

As shown in FIGURE 12, the *ad libitum* animals ignored the taste change produced by corn oil, ingesting equal amounts, on the basis of caloric equivalence of the two diets. On the other hand, the hungry animals ignored the caloric equivalence and increased intake of the medium fat mixture, on the basis of the taste change. Thus, it is clear that hunger potentiates intake via the sensory qualities of the corn oil emulsion.

High Salt Diets. Our final example of diet dilution work in adult rats will be from our analysis of high salt diets. We decided to use salt as a diluent because

it has three characteristics that compliment our work with cellulose. First, it is possible that some of the effects of cellulose may be a function of relative dehydration imposed by gastric absorption of water by the adulterant (Smith *et al.*, 1962). Since NaCl is a known dehydrator, its use as a diluent allows us to assess directly the possible role of osmotic effects in experiments of this type (Jacobs, 1964a). Second, when we started our work with cellulose, we had no direct evidence that taste was involved at all; this had to be inferred from the series of experiments described above. This is not the case with NaCl, since it is well known that this NaCl avoidance is a function of taste, which can be independent of osmotic effects (Stellar *et al.*, 1954; Mook, 1963). In the third place, the high percentage of cellulose diluent necessary to decrease intake significantly increases the unit volume of the diet, thus raising the problem of distention cues, discussed

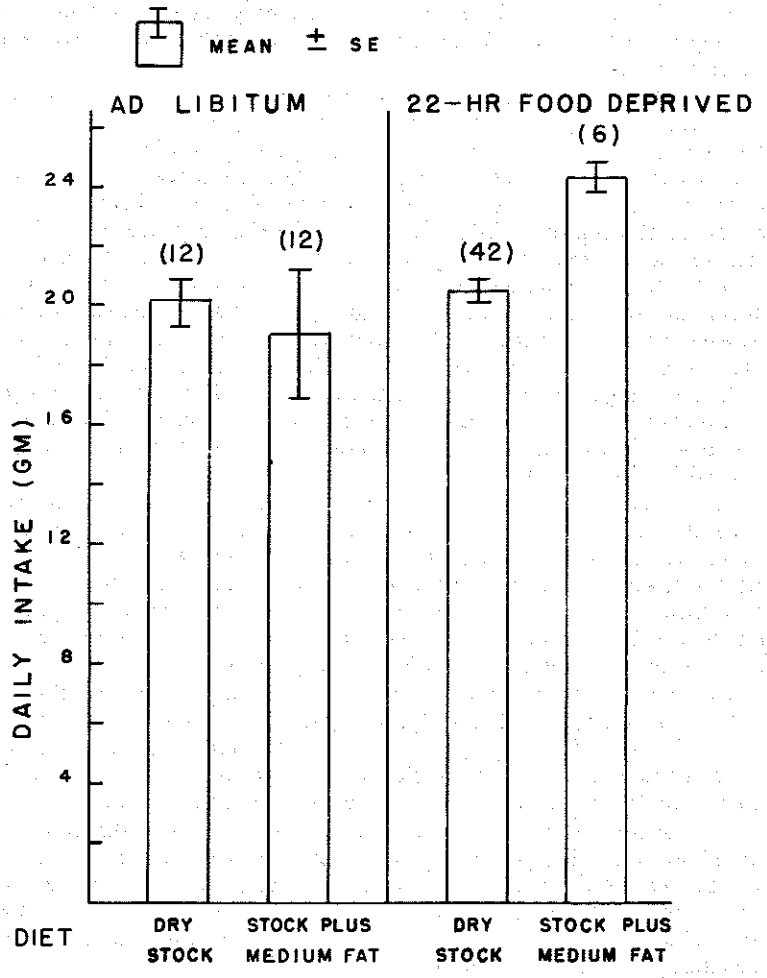

FIGURE 12. Effect of food deprivation on the intake of isocaloric diets (4.00 kcal/g) varying in taste. Parentheses enclose number of observations in each treatment.

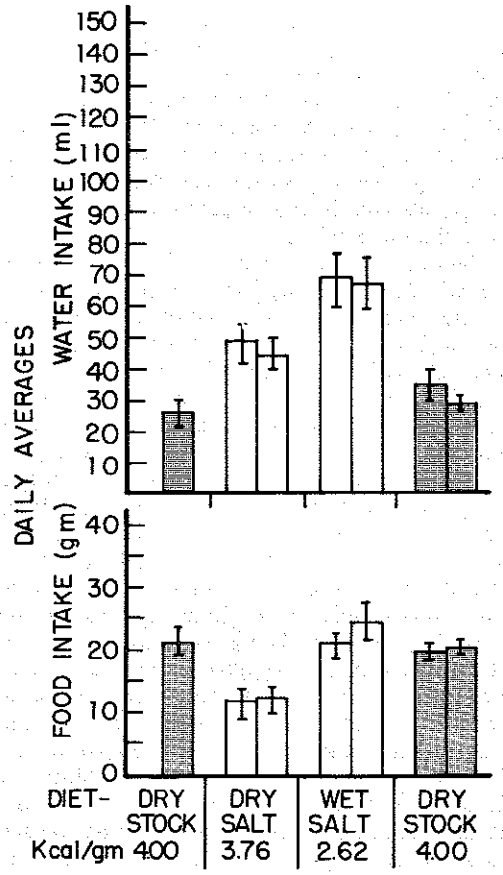

FIGURE 13. Effect of "wetting" on the ingestion of high salt diets (6% NaCl) in hypothalamic hyperphagic rats. Diets "wetted" by adding .8% Tween-80 and 27.7% water. The mean ± SE is plotted on the top of each bar. (Female, N = 5, 75 days postoperative at the beginning of this seven-day series of tests).

above. A "high salt diet" can be obtained with much less than 10% diluent, thus avoiding the distention problem.

In summary, the use of moderate amounts of NaCl provides us with a diluent of known osmotic effects, known deterrent effects on intake based upon negative taste qualities, and one producing minimum changes in volume or caloric value of the diet.

Gamble *et al.* (1929), and Richter and Mosier (1954), have shown that *ad libitum*-fed rats can adapt to dry stock diet containing high concentrations of NaCl. If unlimited drinking water is available, these animals can maintain normal caloric intake and handle the excess salt ingested by appropriate polydipsia and polyuria (Richter & Mosier, 1954). Thus, as in our cellulose dilution experiments, *ad libitum*-fed rats ignore taste, and in this case, osmotic factors as well, and eat for calories. This is not the case with ventromedial-lesioned, obese rats, who decrease their intake when presented with high salt diets (Cort, 1951).

Stevenson *et al.* (1950) and Cort (1951) have observed increased serum sodium in the lesioned, obese rats. If this reflects a relative dehydration, the salt avoidance may merely be a response to the danger of osmotic stress.

Our model offers a simpler alternative, hypothesizing that the finicky lesioned animal avoids salt simply because it is unpalatable. If this is true, two experiments are suggested. First, it should be possible to increase the intake of high-salt diet in lesioned rats by making them more palatable. Second, following our analogy between lesioned, obese rats and the unoperated rat in energy deficit, food deprivation should produce the same effect.

First, the case of the brain-damaged animals. FIGURE 13 shows the daily food and water intake of *ad libitum,* obese, hyperphagic rats tested in the "static" phase of obesity, where "finickiness" presumably is at maximum (Teitelbaum, 1955). Each bar on the Figure presents one day's testing. The dark bars show stock diet intake. The light bars show the intake of high salt diet, containing 6% NaCl. Starting at the left, we see that the obese rats are eating about 20 g of stock diet per day. This is typical in highly obese animals in static hyperphagia, for these animals drop their intake of stock diets close to normal preoperative levels. As we go across the Figure to the second set of bars, we see that the introduction of the high salt diet significantly decreases intake. Note that although food intake is down, these animals increase water intake in response to the osmotic effects of the ingested NaCl; their water/food ratio increased from 1.23 with stock diet to 4.10 with the introduction of NaCl. Continuing to the right of FIGURE 13, we see that the addition of a palatable 28.5% liquid emulsion to the high salt diet increases intake to baseline level, as shown when stock diet is reintroduced on the last two days of the experiment. This effect is not due to the water additive, for the same result can also be obtained by using a corn oil emulsion containing 25% corn oil and only 3% water. Our conclusion is that the initial decrease in intake of high salt diet in the obese rats was not due to osmotic effects, but due to "finickiness" which was overcome when diet palatability was increased. If this is so, our model suggests that one should observe the same phenomenon in normal, hungry rats, in which there is no question of water balance upsets.

FIGURE 14 shows a similar drop in intake in hungry animals when high salt diets are presented. Starting on the left, it is seen that these rats ingest about 18 g of stock per day. When 6% NaCl is added to the diet, they decrease intake to about 10 g per day over a four-day test. Recovery is immediate when stock diet is again available, shown on the right side of the slide. As in the case of the obese animals diagrammed in FIGURE 13, the hungry rat also responds to the osmotic effects of NaCl by increasing relative water intake, the water/food ratio increasing from 2.4 to 5.9 with the introduction of NaCl.

Upon continuing the analogy with the obese animals, it is seen that FIGURE 15 shows that the salt avoidance in hungry rats can be overcome by changing the sensory qualities of the diet. These animals are given six days of testing, starting with dry high salt diet on day 1, and alternating between it and a diet with a palatable high fat additive over the next five days. The increase in high-salt diet intake with the palatable additive on days 2, 4, and 6 of testing is quite consistent. Thus, in agreement with our model, it would appear that taste modulates intake of high salt diets in both brain-damaged and food-deprived animals.

Taste and Caloric Regulation in the Neonate Rat

Gordon Kennedy has accumulated considerable data on the ontogeny of food intake regulation in the rat (Kennedy, 1957 & 1966; Kennedy & Mitra, 1963).

He suggests that young rats lack active satiety systems. For example, the neonate rat can eat enough at least to double average growth rate if competition for food is eliminated by limiting litter size. Further, ventromedial lesions made in weanling animals fail to produce obesity in most rats; obesity eventually does occur, after puberty.

These facts suggest that unoperated neonate rats may be functionally similar to adult obese animals with ventromedial lesions. If this is true, our model would suggest that the neonate is also analogous to the adult animal in energy deficit.

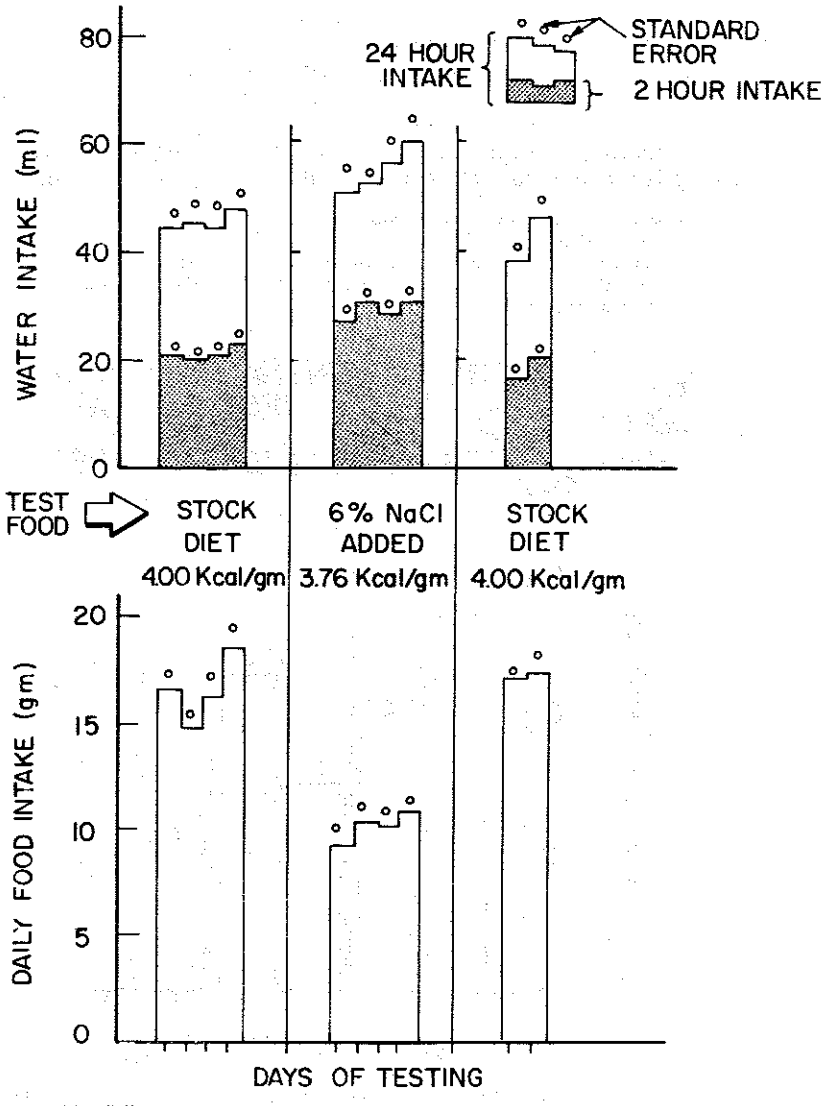

FIGURE 14. Effect of NaCl additive on food and water intake in 22-hour food-deprived rats (N = 14).

Thus, we would expect that if it were possible to study the ontogeny of intake directly in preweanling animals, we would find them failing to regulate for calories and primarily dependent upon taste cues.

The Acceptability Scale. Unfortunately, the neonate rat is too immature to allow direct measure of food intake in individual animals. (We are currently exploring the possibilities of at least partially overcoming this handicap by hand rearing the neonate rats "nurtured" by nonlactating mothers, as described by Miller and Dymza, 1963.) However, preliminary work‡ had suggested that it was possible to measure palatability in individual neonates using solutions in brief exposure tests. The following procedure was developed for use in neonate rats. Within four hours after birth, litters were reduced to the six heaviest animals. Then, through 21 days of age, each litter was removed from the mother for four daily liquid acceptability tests. Single drops of liquid (.01 cc) were applied to the tongue through PE-10 tubing mounted on a 2-cc syringe. Up to five drops of solution was applied over a trial lasting a maximum of 35 seconds. A four category rating scale was used to evaluate acceptability on each trial: (1) maximum

‡ The acceptability scale described in this section was initially developed on the first author's daughter Emily, born in February, 1959. Seventeen hours of palatability testing with glucose, lactose, NaCl, quinine, water, etc., were completed during the first four postnatal days. It is interesting to note that the results obtained in these preliminary observations exactly paralleled those later obtained on neonate rats.

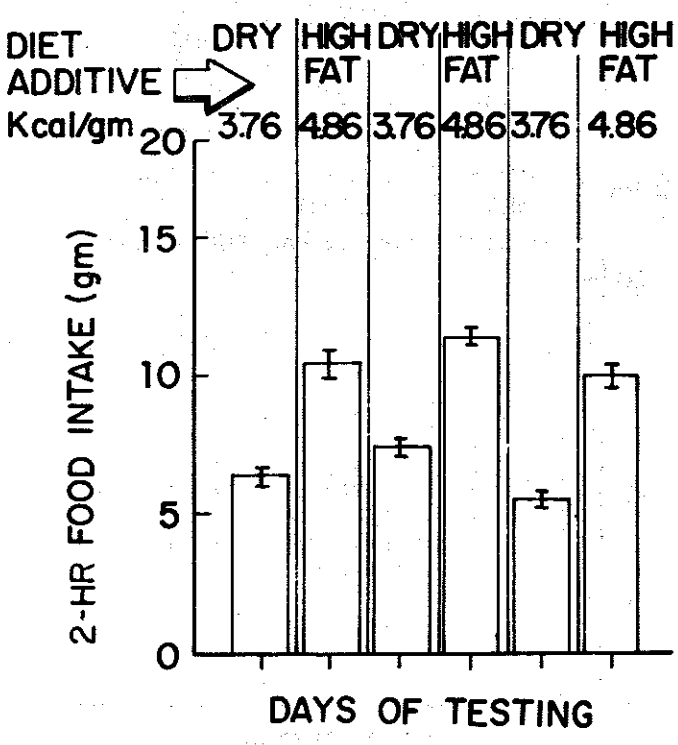

FIGURE 15. Effects of adding high fat emulsions to dry, high salt diets (Containing 6% NaCl) in 22-hour food-deprived rats (N = 14). Additive is 25% corn oil, .8% Tween-80, and 3% water. The mean ± SE is plotted on the top of each bar.

negative: subject (S) struggles, vocalizes, turns and twists head; rapid extrusion of liquid and tube. (2) Medium negative: S is passive, no swallowing, mouth open, tongue retrudes, liquid dribbles out of mouth. (3) Medium positive: S swallows solution, very little overt licking. (4) Maximum positive: S sucks overtly, swallows solution, reaches out for tube when slowly removed, continues licking lips after swallowing. These categories were arranged on a four-point rating scale, ranging from one to four in increasing acceptability. All syringes were coded; thus the experimenters made their ratings without knowldge of the solutions being used. Preliminary work showed that up to four trained experimenters could be used on each litter without significantly affecting the reliability of the acceptability scores.

It should be pointed out that the direct postingestional action of calories in determining acceptability in these experiments was virtually eliminated by our method of testing. Less than .05 ml of test solution per trial was applied to the tongue; thus, the response to all solutions in these tests was primarily due to taste. However, the conditions of nurturing infant rats allowed us to use this technique to pit taste against calories, albeit indirectly. The following argument is applicable.

Analytic Studies. As discussed above, and as demonstrated in FIGURE 4, a very sweet .1% saccharine is palatable to adult rats, and energy deficit significantly increases its palatability, presumably on the basis of taste alone. If our analogue between the adult animal in energy deficit and the neonate rat is correct, we would also expect the neonate rat to demonstrate a very strong innate preference for .1% saccharine, based upon taste alone.

On the other hand, if we assume that the neonate rat eats for calories and is capable of being conditioned during the first three weeks of life, a counter-prediction is possible. Throughout each day of the infants' life, repeated association of the taste of milk with caloric cues available, as hunger is reduced at each feeding period, should accumulate learned incentive value via a simple conditioning process (e.g. Osgood, 1953, p. 439–440). Since the only source of sweetness always available to the neonate rat is the 2.8% lactose occurring in mother's milk, the association of its taste with the nutrient properties of the ingested milk will gradually produce preference for this mildly sweet taste, which will generalize to all sweet tastes to a lesser degree, including the very sweet .1% solution.

FIGURE 16 shows the acceptability ratings during the first three weeks of life for water, .004% quinine (avoided by adult rats), and .1% saccharine. All three solutions start at about 2.5, the neutral point on our acceptability scale. During the 21-day test series, .004% quinine gradually becomes rejected, .1% saccharine becomes accepted, with no significant change for water. The gradual increase in saccharine acceptability looks like a typical learning curve, suggesting that the rats are eating for calories, building up incentive value for the mildly sweet milk, and generalizing to the very sweet saccharine solution. If this is correct, we would also expect a 2.8% lactose solution approximately as sweet as mother's milk to show a learning curve, rising higher and reaching asymptote before the saccharine solution.

FIGURE 17 shows the results of such an experiment, comparing the curves for saccharine and for water with the mildly sweet lactose solution. Lactose was not differentiated from water over the 21 days of testing. Thus, we tentatively concluded that the neonate was not responding to the caloric content of mother's milk, since the taste of lactose failed to be conditioned, but was responding to

saccharine innately, on the basis of its sweetness. If this were true, we should be able to increase acceptability of the lactose solution by making it sweeter. FIGURE 18 shows the results of such an experiment. We chose a 9% sucrose solution, which is highly palatable to adult rats, and paired it with a 17% lactose solution shown to be equal in sweetness in human psychophysical work (Cameron, 1947). The results show that increasing the lactose concentration from 2.8% to 17% increased its acceptability, presumably on the basis of sweetness.

Thus, we would conclude that the acceptability of saccharine is an unlearned response made on the basis of taste cues alone. If this is so, why the apparent "learning curve" for saccharine? Observation of details of the behavior of the neonates suggested that these were really "maturation curves," and that extreme ratings of our acceptability scale required psychomotor coordination requiring several days to develop. We tested this assumption by starting a new series of animals on saccharine tests at 15 days of age. These animals reached asymptote on the first day of testing, showing that practice in tasting saccharine was unnecessary in a more mature rat.

In summary, all of our results were in agreement with the assumption that our neonate rats were responding on the basis of taste. If the animals were responding to calories, they should have shown maximum acceptability for the 2.8% lactose on the basis of learned associations between taste and calories. This did not occur. They responded to the much sweeter saccharine, lactose, and sucrose solution in spite of the fact that they were never associated with calories in the past; all responses were in agreement with the conclusion that they were responding to taste, as suggested by our model.

Common Sense and Quinine Avoidance

In outlining our model in FIGURE 5, we noted that its major assumption is in direct conflict with what we termed the "common sense" view, which argues

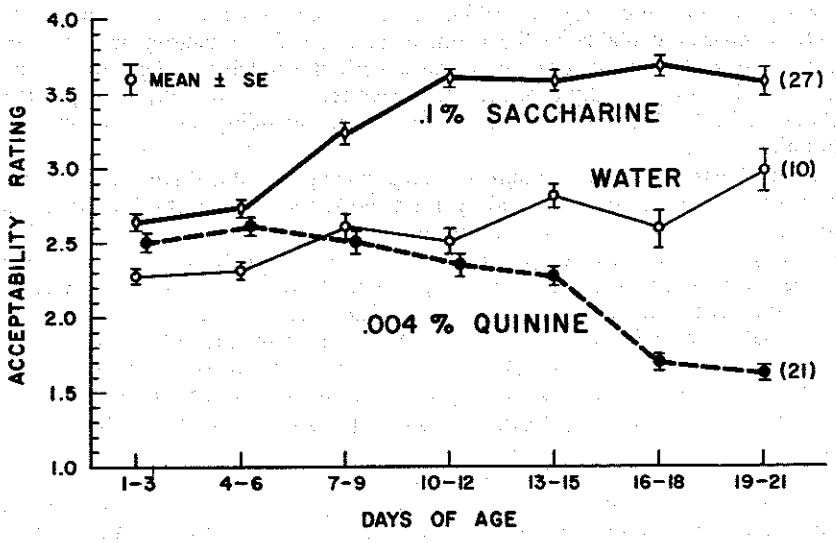

FIGURE 16. Ontogeny of acceptability to "sweet" and "bitter" sensory qualities in preweanling rats. Parentheses enclose number of observations in each treatment.

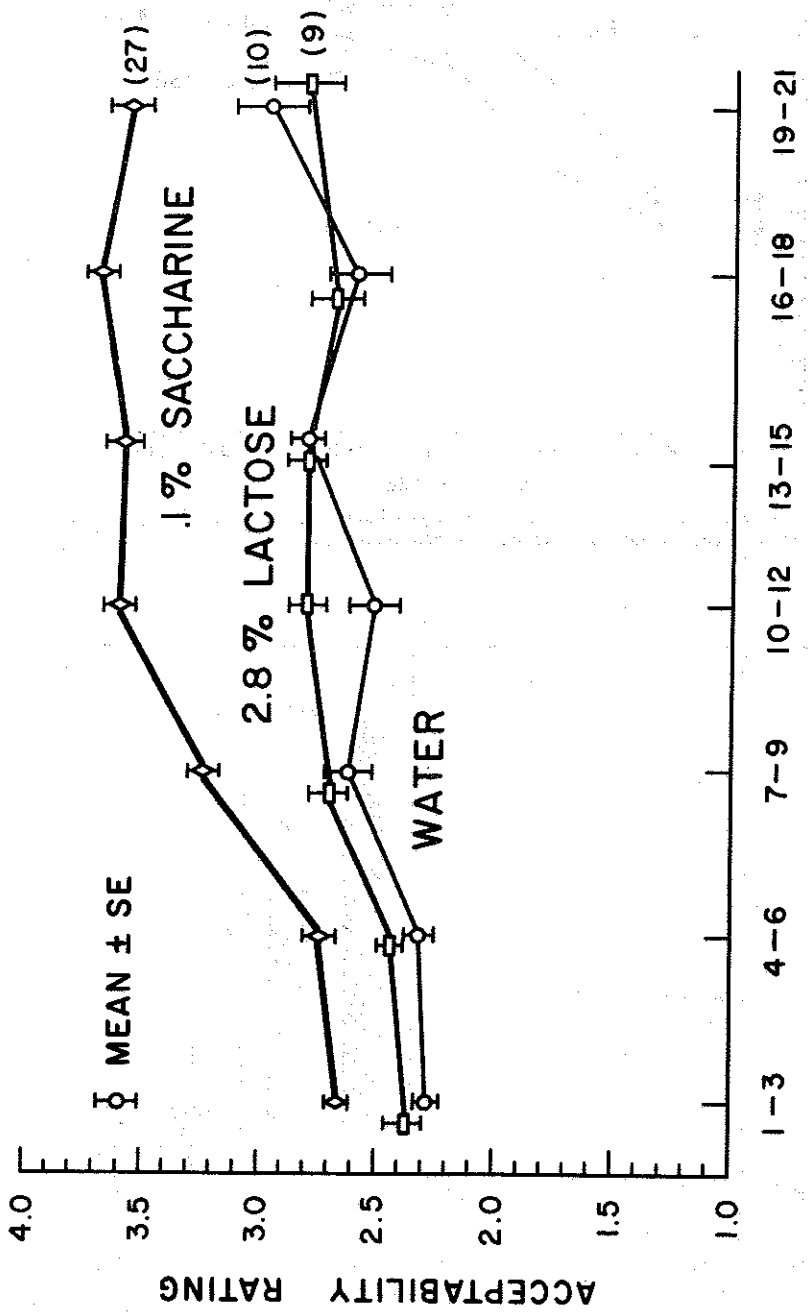

FIGURE 17. Acceptability in preweaning rats of a "mildly sweet" lactose solution equal to that contained in rat's milk and a "sweeter" saccharine solution. Parentheses enclose number of subjects tested in each treatment.

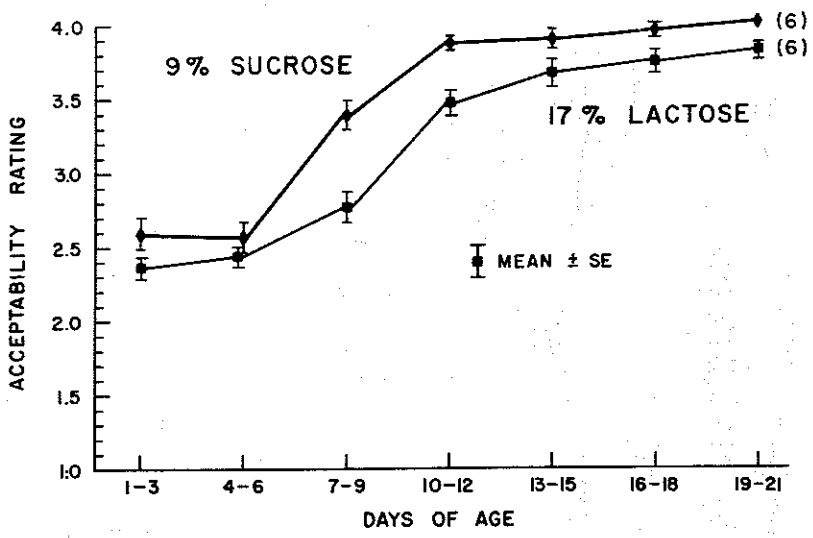

FIGURE 18. Acceptability in preweanling rats of sugars judged "equally sweet" for human observers. Parentheses enclose number of subjects in each treatment.

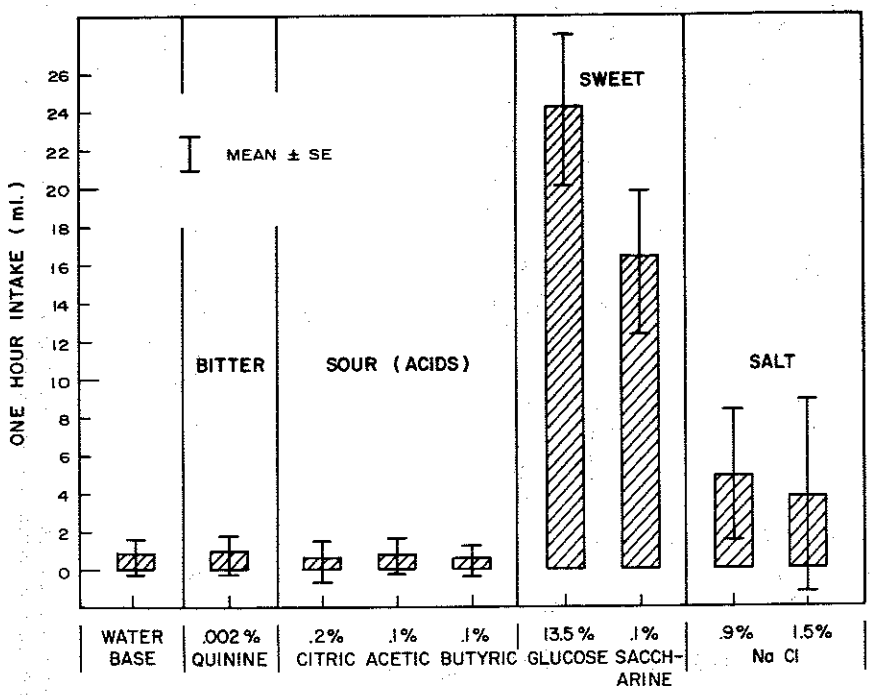

FIGURE 19. Relative preference among classic taste qualities in chronically food-deprived rats (11 g/day). Single-bottle intake tests. (N = 21).

that hunger increases the animal's need so much that it is no longer "choosy" about what it eats. This need not imply that the hungry animal cannot taste the previously unpalatable foods that it now ingests voraciously. It merely asserts that the hungry organism is less discriminating and "cares less" about the sensory aspects of food.

In describing this view, our use of the term "common sense" reflects our judgment that it is an intuitive position buttressed, for the most part, by anecdote rather than hard fact. What kind of laboratory evidence is available to evaluate the common sense view? In our own work, the experiments on pure cellulose intake (see FIGURE 10) failed to confirm it. However, search of the literature does find an excellent series of experiments whose results can be used to defend this view.

In 1956, Miller developed a quinine tolerance test as a measure of hunger motivation in rats. He found that food deprivation sharply increased the amount of quinine necessary to stop milk ingestion in hungry rats (Miller, 1956). Williams and Campbell (1961) and Tenen and Miller (1964) verified and extended these data. These results can be interpreted as showing that hunger does produce more *indiscriminate* eating (e.g. Tenen & Miller, 1964, p. 58).

However, if one follows Miller's suggestion that the quinine tolerance effect may be discussed in terms of conflict behavior (Tenen & Miller, 1964, p. 58), our model offers an acceptable alternative explanation of the same data. The argument can be outlined quite simply. First, we note that the addition of quinine to milk, or to any other palatable food substance produces a complex mixture which can be described in terms of a simple approach-avoidance conflict. In these terms we can assume that quinine provides the avoidance gradient, and milk (or any food) the approach gradient.§ Now, the behavioral evidence that hungry rats have a higher quinine tolerance can be interpreted in two ways: The common sense view would assert that the hungry animal ingests more quinine because the avoidance gradient is lowered. On the other hand, our model would suggest that the hungry animal ingests more quinine because the approach gradient is raised. Thus, our model offers an equally acceptable alternative to common sense, asserting that the rat ingests more quinine, not because it dislikes quinine less (lowered avoidance), but rather, because it likes milk more.

The above analysis led us to design two experiments in an effort to decide between these interpretations. In both experiments we adapted rats to a rather severe deprivation schedule. The animals were given a daily one-hour presentation of a single bottle containing a test solution. This was followed by a one-hour rest period, after which 11 g of food was allowed the animal. Corrections were made to account for any nutrients ingested during solution tests. This schedule produced a stable 20% weight loss in adapted animals.

The first experiment was designed to answer the question of the generality of food deprivation effects on appetite for various solutions. FIGURE 19 shows the results of a series of tests on water, and the four basic taste qualities. Glucose and saccharine showed the greatest effects of food deprivation, presumably on the basis of sweetness (See FIGURE 4). NaCl also showed a significant increase, as previously reported by Kaunitz *et al.* (1960). The three acids, and quinine, showed no hunger effects. Thus, in terms of our conflict analysis it appears that

§ We are using the conflict paradigm in a purely descriptive manner and are not concerned here with its theoretical role in behavior theory. Thus, we could easily have substituted "positive and negative valence" (Lewin, 1935) for "approach and avoidance gradient" (Miller, 1959).

food deprivation increases the approach gradient of "sweet" and "mildly salty" and has no effect on lowering the avoidance gradient of "bitter" and "sour" solutions, which are avoided at these concentrations by *ad libitum* rats as well. Thus, these data are in disagreement with the common sense view in that food deprivation does not make the rat dislike quinine less.

Since our first experiment suggested that there was no change in the avoidance gradient, as required by common sense, we designed a second study to see if changes in the approach gradient could explain the changes in quinine tolerance, as required by our model. This study used the same animals and deprivation schedule described above. Quinine tolerance was measured by starting with .002% quinine sulfate, and adding increments of .04% each day for 26 days, or until three days of complete suppression of intake was observed. The critical part of the experimental design was in our choice of glucose and corn syrup solids as the food bases for the quinine additive. As already discussed, these substances are equal in calories, but vary in taste.

FIGURE 20 shows the results of this series comparing quinine tolerance in glucose or corn-solid mixtures, in *ad libitum,* or in hungry rats.

The *ad libitum* results are shown in the open circles and triangles at the bottom of the Figure. The addition of quinine decreases intake sharply, producing complete depression with the addition of .032% quinine. There is no statistically significant difference between the two curves. Thus, quinine tolerance in *ad libitum* feeding is based upon the caloric equivalence of the solutions and not upon their taste.

The critical test is on the effects of food deprivation, shown in the solid circles and triangles at the top of the Figure. As expected from the results of Miller (1956), hunger significantly increases quinine tolerance for both glucose and

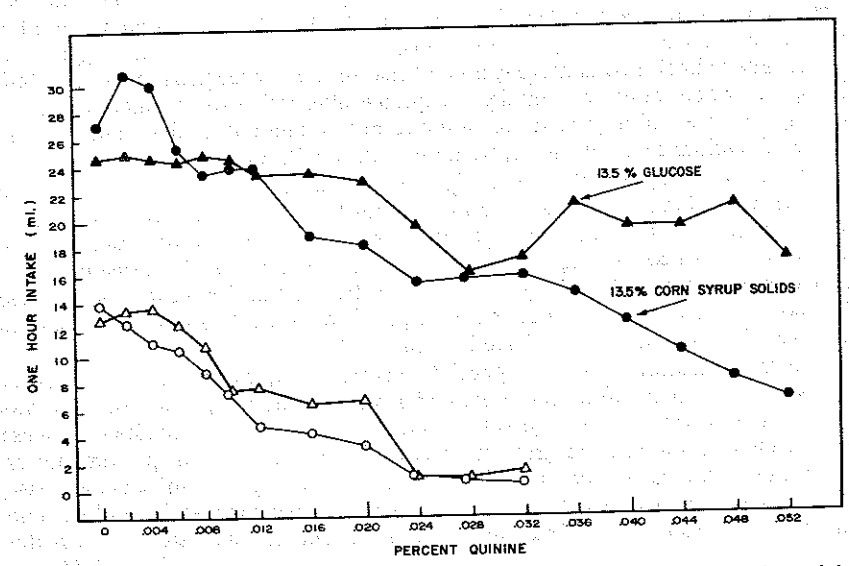

FIGURE 20. Effect of chronic food deprivation (11 g/day) on the tolerance for quinine sulfate added to isocaloric solutions of glucose and corn syrup solids in single-bottle intake tests. (N = 21). Upper curves (dark figures) are food-deprived; lower curves (open figures) are *ad libitum*-fed.

corn solids. The curves for these substances are equal up to the addition of the .032% quinine, after which corn solids continue to drop, showing a 66% decline by the time the very bitter .052% quinine is reached. The glucose solution, on the other hand, levels off with about a 15% depression throughout the rest of the series. The potentiating effect of the addition of .002% quinine to corn solids, as shown in the upper left hand portion of the Figure, is statistically significant, suggesting that small amounts of quinine may actually contribute to the approach gradient in hungry rats.

In summary, quinine tolerance as a measure of appetite differentiated glucose from corn solids under food deprivation, but it failed to do so under *ad libitum* feeding. Since the two solutions are isocaloric, the increased quinine tolerance for glucose in hungry animals apparently is a function of the taste difference.

Combining the results of these two experiments, in terms of our conflict analysis, we see that they are in agreement with the hypothesis that quinine tolerance is higher in hungry rats, not because of any drop in the avoidance gradient, producing indiscriminating eating, but because hunger increases the approach gradient, potentiating the sweet taste of glucose, as required in our model. The same analysis is applicable to the quinine-milk mixtures used by Miller (1956), Tenen and Miller, (1964) and Williams and Campbell (1961).

One final question can be raised by our work on quinine tolerance. How does our analysis of increased quininie tolerance in hungry rats fit in with the observation that ventromedial-lesioned, obese rats, show *decreased* quinine tolerance (Miller *et al.*, 1950; Teitelbaum, 1955). These data suggest that the analogy our model suggests between hungry, unoperated and lesioned, obese rats may be incorrect. However, we should note that all experiments showing decreased quinine tolerance in lesioned animals (Miller *et al.*, 1950; Teitelbaum, 1955) used stock diet as the food base for quinine additive. All the experiments on hungry animals showing increased quinine tolerance (Miller, 1956; Williams & Campbell, 1961; Tenen & Miller, 1964) used liquid food as a base. Perhaps it is not simply a difference of hungry vs. lesioned animals. As shown in FIGURE 8, we also found decreased quinine tolerance in hungry dogs using a stock diet base. This suggests that the liquid food-vs.-stock diet base may be the critical variable. If this is so, one would expect lesioned animals to show *increased* quinine tolerance when quinine is added to a milk base, or a glucose solution base. These data are not yet available, and until they are, it is best to withhold judgment on the usefulness of our analogy between hungry and lesioned rats, at least in the case of quinine tolerance. Although the analogy served us very well in suggesting the experimental series on high salt diets (FIGURES 13, 14, & 15), its usefulness may be limited to a heuristic function.

CONCLUDING REMARKS

In summary, we have described a model in which energy balance is a critical factor in the control of food intake. When the animal is in balance or in surfeit, the metabolic properties of ingested food are critical, and when it is deprived, the sensory properties receive priority in regulating intake. We have summarized some data from the literature which helped us in constructing this model and achieving the results of a program of research carried out to evaluate it.

Looking again at FIGURE 5, we see that all of our *ad libitum*-fed animals would fit on the left side of the model. The right side would contain our hungry dogs, our rats made hungry on food deprivation, or insulin, and our hypothalamic-lesioned obese rats. Our results on appetite for stock diet, high fat, high cellulose,

high salt diets, and positively and negatively flavored solutions are in general agreement with this model. We still consider many aspects of the model to be quite speculative. It is not, however, the type of theory open to disproof via any one crucial experiment. This can also be said of its verification, of course. However, we have found that this model put a heuristic set of working hypotheses in our hands, leading to specific experiments and helping us tie together otherwise unrelated data.

We find that the model raises many interesting general questions. For example, does the deprivation-induced potentiation of taste cues occur via shifts in peripheral sensory thresholds, as Richter (1939) assumes in the case of specific hungers, or via integration in central neuronal circuits? These alternatives are quite speculative, and not relevant at this stage of development of the model. Although the work we reported here is in general agreement with the model, we will continue to modify it as necessary to account for the data that we and others collect. All we are suggesting at this point is that the state of energy balance biases the manner in which the CNS handles sensory or metabolic information, potentiating taste in energy deficit, and calories, when in energy balance or in surfeit.

In addition to the work reported here, we have completed studies on the effect of flavor on the intake of high-protein diets in ventromedial-lesioned and unoperated hungry rats, finding similar responses as in the case of the high-salt diet experiments described here. Our current program of work is developing in three directions: Firstly, electrophysiological studies of information transfer as a function of energy deficit; This will include measures from the gastrointestinal tract, and the classical taste and olfactory paths, as well as in the limbic system; secondly, psychophysical work on human subjects to evaluate sensory and perceptual changes in energy deficit; thirdly, and most important, a program to analyze the term "energy deficit," which I have used in a rather vague and intuitive manner in this paper. We intend to use independent behavioral and metabolic measures of energy balance. We also wish to compare various means of inducing relative energy deficit, including forced exercise, lowered ambient temperature, and injections of thyroxin and DNP.

Finally, we have described our model and the evidence for it in terms of developments in our own laboratory. However, we view our approach as only one of several independent programs of research that are beginning to typify a new bias in the analysis of food and water intake. These groups are beginning to emphasize the short-term as well as long-term controls, the peripheral as well as the central mechanisms, the sensory as well as the metabolic cue systems, and the view of all of these pairs in terms of interaction rather than as dichotomy. Particularly apparent is the increasing attention to the problem of taste, olfaction, flavor, and other sensory qualities, not only as sensory cues, but as integral parts of the actual control of both food intake and metabolic events classically considered on an independent basis. Typical of the details of this trend is the work by DeRuiter, LeMagnen, Nicolaidis, Niijima, and Soulairac in this monograph.

ACKNOWLEDGMENT

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References

Adolph, E. F. 1947. Urges to eat and drink in rats. Amer. J. Physiol. **151**: 110–125.

Beebe-Center, J. B., P. Black, A. C. Hoffman & E. M. Wade. 1948. Relative per diem consumption as a measure of preference in the rat. J. Comp. Physiol. Psychol. **41**: 239–251.

Cameron, A. T. 1947. The taste sense and the relative sweetness of sugars and other sweet substances. NY: Sugar Research Foundation, Scient. Report Series No. 9.

Coppock, H. W. & R. M. Chambers. 1954. Reinforcement of position preference by automatic intravenous injections of glucose. J. Comp. Physiol. Psychol. **47**: 355–357.

Cort, R. L. 1951. The interrelations of hunger and thirst in normal rats and rats with hypothalamic lesions. Unpublished thesis for Doctor of Medicine, Yale University, New Haven.

Cowgill, G. 1928. The energy factor in relation to food intake: Experiments on the dog. Amer. J. Physiol. **85**: 45–64.

Epstein, A. N. & P. Teitelbaum. 1962. Regulation of food intake in the absence of taste, smell and other oropharyngeal sensations. J. Comp. Physiol. Psychol. **55**: 753–759.

Gamble, J. L., M. C. Putnam & C. F. McKhann. 1929. The optimal water requirements in renal function. I. Measurement of water intake by rats according to increments of urea and several salts in the food. Amer. J. Physiol. **88**: 571–580.

Jacobs, H. L. 1961. Taste versus calories as modulators of glucose intake. Fed. Proc. **20**: 207.

Jacobs, H. L. 1962. Some physical, metabolic, and sensory components in the appetite for glucose. Amer. J. Physiol. **203**: 1043–1054.

Jacobs, H. L. 1963. Evidence for a bipolar detector system involved in hunger and satiety. The Physiol. **6**: 209.

Jacobs, H. L. 1964. Observations on the ontogeny of saccharine preference in the neonate rats. Psychonom. Sci. **1**: 105–106.

Jacobs, H. L. 1964a. The interaction of hunger and thirst: Experimental separation of osmotic and oral-gastric factors in the regulation of caloric intake. *In* Thirst Symposium. Wayner, M., Ed. : 117–137. Pergamon. Oxford.

Jacobs, H. L. 1966. Sensory and metabolic regulation of food intake: Thoughts on a dual system regulated by energy balance. *In* Proc. VII Inter. Cong. Nutrition Vol. II. Regulation of Hunger and Satiety : 17–29. Pergamon. Oxford.

Jacobs, H. L. 1967. Taste and the role of experience in the regulation of food intake. *In* The Chemical Senses and the Nutritive Processes. Kare, M. & Maller, O., Eds. : 187–200. John Hopkins Press. Baltimore, Md.

Jacobs, H. L. & K. N. Sharma. 1964. Energy balance and palatability: The effect of food deprivation on the intake of positively and negatively flavored solutions. The Physiol. **7**: 166.

Jacobs, H. L. & K. N. Sharma. 1964a. The modulating influence of flavor on food preferences in hypothalamic obese rats. Fed. Proc. **23**: 448.

Jacobs, H. L., K. N. Sharma & S. Dua-Sharma. 1965. Energy balance and feeding behavior: The effect of food deprivation on the intake of high salt diets. Proc. Int. Cong. Physiol. Sciences, Tokyo, Sept. 1–9. P. 226.

Janowitz, H. D., M. E. Hanson & M. I. Grossman. 1949. Effect of intravenously administered glucose on food intake in the dog. Amer. J. Physiol. **156**: 87–91.

Janowitz, H. D. & M. I. Grossman. 1949. Effect of variations in nutritive density on intake of food of dogs and rats. Amer. J. Physiol. **158**: 184–193.

Janowitz, H. D. & F. Hollander. 1955. The time factor in the adjustment of food intake to varied caloric requirement in the dog: A study of the precision of appetite regulation. *In* The Regulation of Hunger and Appetite. Hollander, Ed. Annals N. Y. Acad. Sci. **63**: 56–67.

Kare, M. R. 1961. Comparative aspects of the sense of taste. *In* The Physiological and Behavioral Aspects of Taste. Kare, M. R. and Halpern, Eds. : 6–15. Univ. of Chicago Press. Chicago.

Katz, D. 1963. Animals and Men. (Transl. from the 1948 rev. Ed.) Pelican. London.

Kaunitz, H., L. M. Geller, C. A. Slanetz & R. E. Johnson. 1960. Food Restrictions and salt preference in rats. Nature **185**: 350–353.

Kennedy, G. C. 1957. The development with age of hypothalamic restraint upon the appetite of the rat. J. Endocrinol. **16**: 9–17.

Kennedy, G. C. 1966. Food intake, energy balance, and growth. Brit. Med. Bull. **22**: 216–221.

KENNEDY, G. C. & J. MITRA. 1963. Body weight and food intake as initiating factors for puberty in the rats. J. Physiol. **166:** 408–418.
LEMAGNEN, J. 1954. Le processus de discrimination par le rat blanc des stimuli sucres alimentaires et non alimentaires. J. Physiol. **46:** 414–418.
LEMAGNEN, J. 1963. Le control sensorial dan la régulation de l'apport alimentaire. Extrait De "L'Obésité," Expansion Scientifique, ed. Paris. 147–171.
LEMAGNEN, J. & H. PIERON. 1953. Activité de l'insulin sur la consommation spontané des solutions sapides. C. R. Soc. Biol. **147:** 1753–1756.
LEWIN, K. 1935. A dynamic theory of personality: Selected papers (trans. by Adams, D. K. & K. E. Zener). McGraw-Hill. New York.
MCCAY, C. M., J. C. WOODWARD & B. S. SCHGAL. 1934. Cellulose in the diet of rats and mice. J. Nutrition **8:** 435–447.
MILLER, N. E. 1956. Effects of drugs on motivation: The value of using a variety of measures. Annals N. Y. Acad. Sci. **65:** 318–333.
MILLER, N. E. 1959. Liberalization of basic S-R concepts: Extensions to conflict behavior, motivation, and social learning. *In* Psychology: A study of a science. S. Koch, Ed. : 196–292. Vol. **II:** 196–292. McGraw-Hill, New York.
MILLER, N. E., C. J. BAILEY & J. A. F. STEVENSON. 1950. Decreased "hunger" but increased food intake resulting from hypothalamic lesions. Science **112:** 256–259.
MILLER, S. A. & H. A. DYMSZA. 1963. Artificial feeding of neonate rats. Science **141:** 517–518.
MOOK, D. 1963. Oral and postingestinal determinants of various solutions in rats with esophageal fistulas. J. Comp. Physiol. Psychol. **56:** 645–659.
OSGOOD, C. 1953. Method and theory in experimental psychology. Oxford. New York.
PANGBORN, R. M. 1964. Palatability, food intake, and obesity. J. Obesity. **1:** 13–15.
PFAFFMAN, C. & E. C. HAGSTROM. 1959. The relative taste effectiveness of different sugars for the rat. J. Comp. Physiol. Psychol. **52:** 259–262.
RICHTER, C. P. 1939. Salt-taste thresholds of normal and adrenalectomized rats. Endocrinol. **24:** 367–371.
RICHTER, C. P. & H. D. MOSIER. 1954. Maximum sodium chloride intake and thirst in domesticated and wild Norway rats. Amer. J. Physiol. **176:** 213–222.
SCOTT, E. M. 1948. Self-selection of diet. Trans. Amer. Assoc. Cereal Chemists **6:** 126–133.
SCOTT, E. M. & ELEANOR QUINT. 1946. Self selection of diet. II. The effect of flavor. J. Nutrition. **32:** 113–119.
SEBRELL, W. H. 1961. The prospect of meeting protein needs. *In* Proc. of the Fifth Int. Cong. of Nutrition. Fed. Proc. **20:** 393–397.
SMITH, N., R. POOL & H. WEINBERG. 1962. The role of bulk in the control of eating. J. Comp. Physiol. Psychol. **55:** 115–120.
SOULAIRAC, A. 1944. Action de l'insuline sur la consummation de différents glucides chez la souris. Comt. Rend. Soc. Biol. **138:** 119–120.
STELLAR, E., R. HYMAN & S. SAMET. 1954. Gastric factors controlling water and salt. J. Comp. Physiol. Psychol. **47:** 220–226.
STEVENSON, J. A. F., L. G. WELT & J. ORLOFF. 1950. Abnormalities of water and electrolyte metabolism in rats with electrolytic lesions. Amer. J. Physiol. **161:** 35–39.
STROMINGER, J. L., J. R. BROBECK & R. L. CORT. 1953. Regulation of food intake in normal rats and in rats with hypothalamic hyperphagia. Yale J. Biol. Med. **26:** 55–74.
TATEDA, H. & I. HIDAKA. 1966. Taste responses to sweet substances in rat. Memoirs of the Faculty of Science, Kyushu Univ., Series E. (Biology) **4:** 137–149.
TEITELBAUM, P. 1955. Sensory control of hypothalamic hyperphagia. J. Comp. Physiol. Psychol. **48:** 156–163.
TEITELBAUM, P. & A. N. EPSTEIN. 1963. The role of taste and smell in the regulation of food and water intake. *In* Olfaction and Taste. Y. Zutteeman, Ed. Vol. I: 347–360. Pergamon. London.
TENEN, S. S. & N. E. MILLER. 1964. Strength of electrical stimulation of lateral hypothalamus, food deprivation, and tolerance for quinine in food. J. Comp. Physiol. Psychol. **58:** 55–62.
WILLIAMS, R. A. & B. A. CAMPBELL. 1961. Weight loss and quinine milk ingestion as measures of "hunger" in infant and adult rats. J. Comp. Physiol. Psychol. **54:** 220–222.
YOUNG, P. T. 1948. Appetite, palatability, and feeding habit. A critical review. Psychol. Bull. : 289–320.

DISCUSSION

S. BALAGURA: In light of the way Dr. Jacobs classifies metabolic and sensory

mechanisms involved in regulating food and water intake, it is interesting to note that both the metabolic and osmotic properties of glucose (one of the most important carbohydrates of the bioenergetic cycle in the animal cell) could be sensed by the organism. A controversy has centered on this issue. To examine the differential effects of these two properties of glucose, the following experiment was conducted: Rats with electrodes in the lateral hypothalamic area were injected with 3 cc of one of the following solutions, 0.3 Osm saline (control), 2.0 Osm glucose or 2.0 Osm saline. Immediately following the load, they were allowed to self-stimulate for two hours. During the test period the animals had free access to water. FIGURE 1 shows the results obtained for five animals: self-stimulation rate decreased significantly from the control level (C) in the animals injected with hypertonic glucose (G) or saline (S), but only those injected with hypertonic saline drank great quantities of water. The results suggest that although both hypertonic glucose and saline decreased self-stimulation rate, hypertonic

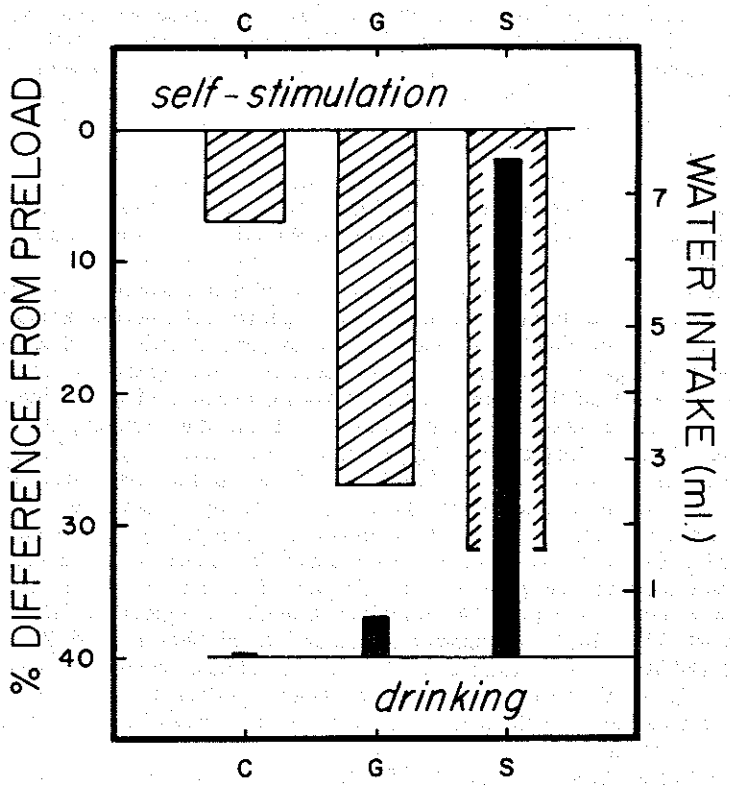

FIGURE 1. Differential effects of hypertonic glucose and NaCl loads on lateral hypothalamic self-stimulation rate (left ordinate) and on water intake (right ordinate) in a two-hour test period (N = 5 rats). (L) control, .3 Osm. NaCl, (G) 2.0 Osm. glucose, and (S) 2.0 Osm. NaCl.

saline decreased it because of its osmotic properties, while glucose acted in a different way, probably due to its metabolic properties.

DR. JACOBS: Your results are in agreement with our previous work on the satiating effects of glucose and NaCl on the intake of glucose solutions (Jacobs, H. L. The Osmotic Postingestion Factor in The Regulation of Glucose Appetite *In* (The Physiological and Behavioral Aspects of Taste. Kare, M. & Halpern, B. Eds., Univ. Chicago Press. 1961. pp. 16–28) or of dry stock diet (Jacobs, H. L. Evaluation of The Osmotic Effects of Glucose Loads in Food Satiation. J. Comp. Physiol. Psychol., **57:** 309–310. 1964). In these studies we also concluded that the glucose effects were metabolic rather than osmotic. One still unresolved question concerns the demonstrated satiety effect of hypertonic NaCl on the intake of glucose, or of dry diets, or, in your data, on self-stimulation rates. Does this mean that we have at least two sets of satiety signals, one typified by glucose (metabolic), and one by NaCl (osmotic)? In our own work, we have often observed that the apparent satiety induced by hypertonic NaCl loads may be compounded by malaise from load stress. This possible interpretation should be analyzed further before concluding that NaCl-induced osmotic effects necessarily induce voluntary satiation.

DR. MOOK: Does the Tween emulsifier you have used cause diarrhea? We have observed severe diarrhea when using liquid diets containing the emulsifier.

DR. JACOBS: No, not in the amounts our animals ingest; the diet mixtures we used contained a maximum of only 0.9% Tween-80. Perhaps the difference might be attributed to the fact that our diets were equivalent to wet mash rather than liquid.

DR. MOOK: My second question concerns the parallel you draw between the food-deprived rat and the hyperphagic. The hyperphagic rat shows "finickiness" after it is obese, not while it is gaining weight. Wouldn't your suggestion predict the opposite?

DR. JACOBS: The model I outlined here grew out of a program of work in which our major interest has been in the analysis of appetite in the normal animal. We have thought of the finicky, lesioned animal in general terms, and have not pressed our analogue to include the specific prediction you suggest. We preferred to be conservative on this point for the following reasons. First, the literature on the ventromedial-lesioned animal shows that the data relating the terms "dynamic," "static," "obese," and "hyperphagia," are not at all clear. Let me list some examples: First, although Teitelbaum failed to find finickiness in the dynamic phase, his animals were made experimentally dynamic by repeated bouts of forced weight reduction (P. Teitelbaum, J. Comp. Physiol. Psychol. **48:** 156, 1965). However, it *is* possible to show sensitivity to taste when "dynamic' is defined as the initial postoperative phase for *ad libitum*-fed rats. Using this type of dynamic animal, Soulairac (A. Soulairac, Bulletin Biologique of France and Belgium, 81, 397, 1947) and Jacobs (H. Jacobs & K. N. Sharma, Fed. Proc. **23:** 448, 1964.) have found an exaggerated glucose preference, *which disappeared in the static phase.* We have also found the dynamic animal to be as finicky as static animals when presented with the high salt diets described in this paper. Finally, it is possible to show finickiness without hyperphagia (H. Graff & E. Stellar, J. Comp. Physiol. Psychol. **55:** 418, 1962), as well as finickiness in obese, nonlesioned animals (O. Maller, Life Sciences **3:** 1281, 1964). These facts make it clear that much more experimental analysis of the brain-lesioned animal is needed to resolve some of these apparent contradictions. This will require a broad behavioral analysis. Although most of us have paid lip service to

the generalization that the brain-lesioned, hyperphagic and/or obese rat is a very complex preparation, and that the upset in food intake is only one component in a broad syndrome, most of us have ignored it because of our interest in feeding behavior.

DR. HAMILTON: Your hungry dogs took less quinine than did *ad lib* controls, while our eight-day fasted rats did not take less quinine than our *ad lib* controls, even though they demonstrated starvation anorexia with stock diet. Thus, your deprived dogs were *more* finicky, while our deprived rats were *less* finicky. Could you comment on this contradiction?

So much more work has been done with the rat than with the dog, as regards intake of food, that I am wondering if you could tell us of any important differences that you have found other than those we are just now reporting between food intake in the dog and in the rat.

DR. JACOBS: I could do no more than speculate on the reason for the differences that we obtained. Two procedural differences come to mind. Firstly, you used a single eight-day starvation period that produced limited baseline intake of stock diet due to starvation anorexia; our dogs were thoroughly adapted to the 15-minute daily meal and were ingesting stock diet maximally. Secondly, you added powdered quinine to a dry stock diet; we put it into solution, and then added 70% of this liquid to stock diet to produce our feeding mixture. A repetition of our experiments, exchanging procedures on these two points, may be helpful in clarifying this matter.

As to species differences, we tested our dogs with cellulose dilution, fat dilution, and diets of varying texture and found no striking differences between dog and rat. One exception was that we found much more daily variability in food intake with our forced *ad lib* dogs under all diets than under comparable conditions with *ad lib* rats.

Studies on thirst have shown sharp differences between dog and rat, of course. As Adolph and others have noted, dogs drink very rapidly and make up water deficits quite accurately, but fail to decrease intake in proportion to gastic water loads, while rats drink much more slowly, are sluggish in making up a deficit, and respond quickly to gastric water loads. (See Wolfe, A. V. *Thirst.* C. C. Thomas. Springfield. 1958. pp. 146–162). Thus, it has been suggested that the dog is metering orally and the rat is metering gastrically. However, to complicate things, the burro, camel, and young rabbit also act like the dog, whereas the hamster, guinea pig, and adult rabbit act like the rat.

These are all isolated observations, of course. You are correct in noting that much more work has been done in the rat than in the dog, or in any of these animals. This is an unfortunate stiuation, to which I have also contributed, of course. The experiments I reported here were the first in which I have used a "non-rat" animal subject. One of the really great needs in this field is a precise analysis of species differences. Your work on the control of intake in monkeys is an excellent example of this (Hamilton, C. L. & J. R. Brobeck. Annals N.Y. Acad. Sci. **131:** 583–592, 1965).

The need for *intraspecies* comparative work is just as important. Dr. Valenstein's beautiful analysis of sex differences in the effects of ventromedial damage (reported in this monograph) is one example. Let me outline another, related to your initial question.

In your paper, you pointed out that you used the Charles River strain of Sprague-Dawley rats. As you presented your data, I was as interested in your *ad lib* rats as you were in my hungry dogs, for they had an initial daily intake of

26.5 g of stock diet, which dropped significantly to 18.0 g with quinine dilution. From my point of view, your *ad lib* animals were quite finicky. This would also appear to be contrary to what we would expect from our model, for we assume that caloric regulation is more important when in energy balance.

Perhaps your finicky response to quinine was due to the fact that this was only a one-day test? However, our own experience with Charles River animals would suggest otherwise. All of the results on *ad lib* rats that we presented today were on Holtzman rats of the Wistar strain. We used the Charles River rats for the first time this past summer and were disconcerted to find that in a long series of two-day tests, our *ad lib* rats were just as sensitive to taste as were our food-deprived groups. This made it difficult to get a baseline to evaluate the effects of deprivation.

During these experiments, we noted that our Charles River *ad lib* controls were extremely large rats, much larger than any other Sprague-Dawley animals we had ever used in the past. Sherman has compared Charles River animals to three other strains and found that they are much heavier (more than 800 g average maximum weight for males); his data suggest that this is due to increased intake rather than to changes in food efficiency (Sherman, H. Lab. Anim. Care. **13:** 793–807, 1963).

These facts suggest that the Charles River rat could be described as a *spontaneously occurring obese hyperphagic*. This is just speculation at present, but it suggests that studies of finickiness in unoperated, *ad lib*-fed Charles River rats, may produce some interesting results.

Although we have emphasized energy deficit as critical in shifting from caloric to taste regulation in our model, evolution may have produced species that tend to be finicky under other specified conditions. Mrosovsky's interesting analysis of finickiness in dormice, ground squirrels, and hamsters suggests that prehibernation obesity may be mediated by a reversible change in the function of the satiety center, analogous to the changes produced in lesioned rats. (Mrosovsky, N. Anim. Behav. **12:** 454–469, 1964). We would speculate that the change is also analogous to those occurring in our animals in relative energy deficit.

A comparative approach to these issues may also uncover species that tend to be finicky all of the time. The baseline we used in developing our model happened to be the domestic albino rat, which adjusts very well to diet dilution. We would have obtained quite different results had we used the opossum. Maller *et al.*, found that *ad lib*-fed opossums respond very sluggishly to cellulose dilution or fat enrichment (Maller, O., J. M. Clark & M. R. Kare, Proc. Soc. Exp. Biol. Med. **118:** 275–277, 1965). In fact, the response to cellulose dilution was much like that of a hyperphagic rat, or our food-deprived, or insulin-injected animals.

The constructively teleological reasoning that these authors used to explain their results is quite interesting: "Rigid caloric regulation would be of limited value to an animal with an irregular and varied food supply. A sensitivity to palatability would be of greater consequence to a wild animal than to a domesticated animal, where rapid detection and discrimination among nutrients has less survival value." (Maller *et al.*, p. 277).

We could apply the same argument to our food-deprived rat that is shifted from an economy of plenty (*ad lib* feeding) to an economy of scarcity. The constant 22-hour deprivation schedule used in our experiments produced scarcity with a constant food supply. Gross recently extended this line of reasoning by using a random deprivation schedule (ranging from 2–48 hours and averaging 22 hours)

producing scarcity plus an irregular and varied food supply. This random deprivation schedule made rats significantly more responsive to the sensory qualities of diets diluted with fat, or cellulose. (See Gross, L. Scarcity, unpredictability, and eating in rats. Ph.d Thesis, Columbia Univ., 1968.)

This has been an overly tedious comment on your question, Dr. Hamilton, raising more issues than it resolved. However, if questions of this type can stimulate more of us to undertake comparative analyses of food and water intake, it will have been worth it.

DR. VALENSTEIN: I would like to compliment Dr. Jacobs on the presentation of his very interesting experiments demonstrating the importance of taste factors, particularly with hungry animals. Evidence such as that presented by him emphasizes that the choice of foods can not rest primarily on the postingestional reduction of bodily needs. Indeed, the time delay before any benefit could be derived from the substance ingested forces one to conclude that such a mechanism would be most inefficient for guiding ongoing behavior.

We have completed several experiments with glucose and saccharin solutions and have concluded that in animals deprived of food, palatibility may play a more dominant role than caloric value (Valenstein, E. S., J. Comp. Physiol. Psychol. **63:** 429–433, 1967).

In our experiments animals are provided with both a very sweet, but noncaloric .25% sodium saccharin solution and a mildly sweet, but caloric 3% glucose solution. Twenty-four-hour consumption is measured over successive days when the animals have food available *ad libitum* (satiated condition) and for only 75 minutes each day (hungry condition). FIGURE 1 shows that when satiated for food, the animals first prefer the sweeter saccharin solution, but after several days they switch to a glucose preference. This pattern is characteristic of male rats and has been replicated a number of times (Valenstein and colleagues.

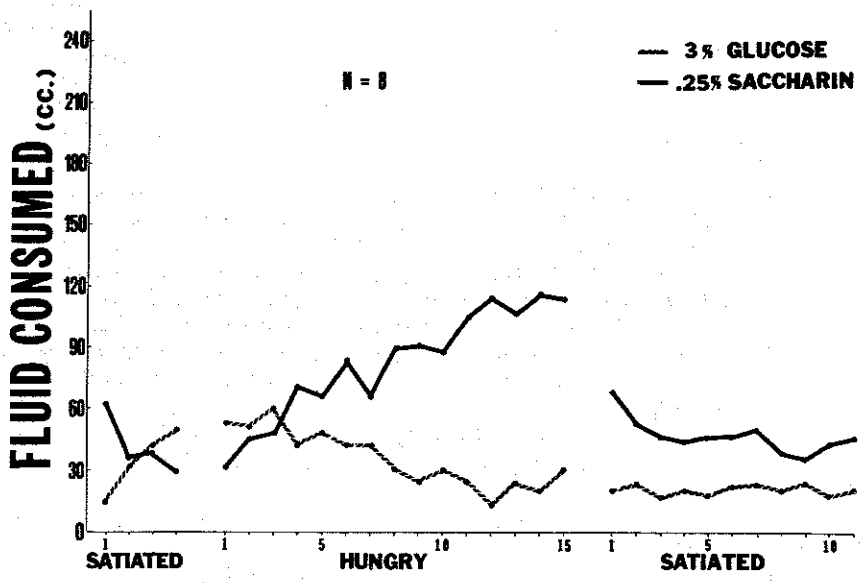

FIGURE 1. Daily consumption chartered in two-day averages of 3% glucose and .25% saccharin during satiated and hungry conditions.

Science **156:** 942–943, 1967). However, when the animals are deprived of food, they gradually switch back to a saccharin preference, which becomes increasingly greater over a 30-day period in the hungry condition. It is especially striking that most animals not only increase their consumption of saccharin when they are hungry but also decrease the amount of glucose solution consumed, thereby reducing their caloric intake. Complementing these findings is a study performed in our laboratory in which animals were deprived of food for 24 hours before the glucose and saccharin solutions were made available to them. Thereafter, food was provided for only 75 minutes each day. These animals did not switch to a glucose preference, as do satiated animals, but instead consumed large amounts of the saccharin solution and over seven days of observation consumed only minimal (8 cc per day) amounts of the glucose solution. Several of the animals of this group died of starvation, but prior to this exhibited no tendency to switch to the glucose solution. This is considerably more loyalty than that exhibited by those individuals in the cigarette advertisements who "would rather fight than switch."

Following the hungry condition, when food is once again provided *ad libitum*, the animals reduce their consumption of the saccharin solution but maintain a preference for this solution over a 22-day period (FIGURE 1). These last results suggest a relatively permanent change (within the limits of our observation period) produced by the 30 days of high levels of saccharin consumption.

These results have been replicated in our laboratory, but we also see animals that increase their consumption of glucose when deprived. If this pattern is adopted, animals may not actually experience hunger because of the caloric contents of the glucose and consequently, may not switch to a saccharin preference. FIGURE 2 presents the results in an animal showing an "intermediate response pattern." During the food-deprivation period this animal increased its consumption of both glucose and saccharin solution but maintained a preference for the glucose for ten days. On days 11 and 12 the animal switched to a saccharin preference. At this point we decreased the caloric intake of the animal by maintaining the 75-minute feeding schedule, but offering only water for the next two days. When the animal was once more provided with the glucose and saccharin solutions on hunger days 15–18, the preference for the saccharin was significantly increased.

In the same experimental conditions a few food-deprived animals displayed a gradual increase in consumption of the glucose solution, which could not be reversed by a more severe state of deprivation. It is possible that some animals learn to associate the glucose with the delayed attenuation of their hunger state. In this context, Dr. Paul Rozin has studied the feeding pattern of rats offered a "cafeteria" array of substances when deprived of a specific bodily requirement. Many of these animals adopt a pattern of ingesting one substance exclusively for a time long enough to permit them to select the beneficial food even if taste factors cannot be operating.

There is considerable evidence stressing the importance of the motivational state elicited directly by oropharyngeal sensations. Animals eat what they like and because of evolutionary selection they tend to like what is good for them. If the world had been filled with 3% glucose and .25% saccharin solutions, animals would have evolved differently.

I would raise two questions in connection with Dr. Jacob's conclusion that an "animal eats for calories when he does not need them, and eats for taste when he needs calories." Is it possible that this conclusion results from a limited array

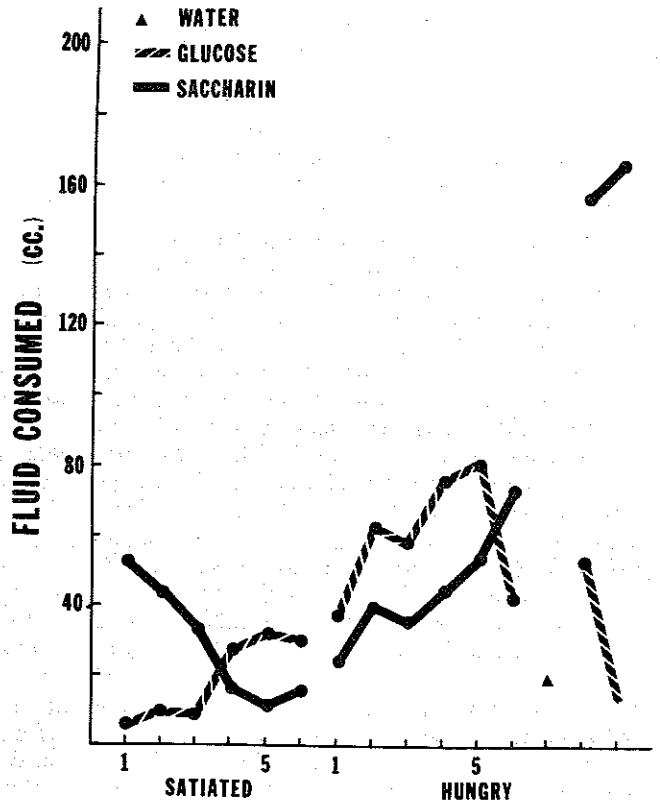

FIGURE 2. Daily consumption chartered in two-day averages of 3% glucose and .25% saccharin during satiated and hungry conditions. Data based on performance of an animal exhibiting an "intermediate response pattern" (cf. text).

of substances used in experiments to date and that an animal eats for taste when both satiated and hungry, but that taste preferences differ; and is it possible that the same mechanisms are not brought into play in the regulation of different substances?

DR. JACOBS: First, a comment on the experiment you report, for it clarifies the one clear exception I know to the generalization that energy deficit potentiates taste rather than calories. In 1953, W. T. Griffiths and T. J. Gallagher (Science **118:** 780, 1953) forced rats to swim for 110 minutes and gave them a choice among 20% glucose, .15% saccharine, water and stock diet. They found an increased preference for glucose with no change in saccharine intake and concluded that the rats were not fooled by saccharine, ingesting more glucose because it provided calories.

Although the conclusions were logically correct, I have since wondered about an alternative explanation, which assumes that the "hungry" rats preferred 20% glucose merely because it was sweeter. The results of your experiment are consistent with this alternative: by decreasing the sweetness of the glucose, you were able to shift the preference to a sweeter saccharine solution, regardless of the absence of calories.

Now to your question about my statement that satiated animals eat for calories. I agree that it is unlikely that postabsorptive metabolic signals, or what the psychologist has classically called "need reduction," ever acts alone to determine intake. However, one must take account of the fact that *ad libitum* animals do adjust intake to caloric density, such as cases in your FIGURE 1, where your satiated rats prefer the nutrient, glucose, to saccharine. Experiments of this type, in which taste and nutrient qualities are varied independently, demonstrate that rats can follow caloric cues, ignore taste cues, or in the case of chronic intragastric feeding, apparently dispense with oropharyngeal sensations entirely (Epstein, A. N. & P. Teitelbaum. J. Comp. Physiol. Psychol. **55:** 753–759, 1962). Thus, I would say that the *ad libitum* animal "eats for calories." This does not imply that the satiated animal is using the slow-acting postabsorptive caloric signals. There is increasing evidence that fast-acting chemoreceptor systems responsive to metabolic properties of food are located in the GI tract. (Sudakov, K. V. & S. K. Rogacheva. Fiziol. Zhurnal SSSR I. M. Sechnova **48:** 758, 1962; Chernigovsky, V. N. Pavlov J. Higher Nerv. Activity **10:** 313, 1960; Sharma, K. N. & E. S. Nassett. Amer. J. Physiol. **202:** 725–730, 1962; also see Niijima's paper in this monograph. The mechanism of "eating for calories" may well involve these fast-acting systems.

One final point. Although satiated animals can eat for calories in the sense outlined above, flavor is still important, in at least three ways. First, to help discriminate edible from nonedible objects; second, as P. T. Young has emphasized in many papers, palatability can be innately determined; third, as Dr. LeMagnen will show in his paper, flavor can act as a guide to caloric content through the mechanism of conditioning.

DR. COLLIER: As you know, we have done a number of experiments on the rate of bar-pressing for solutions such as sucrose, saccharin, or milk differing in concentration with animals differing in the degree of hunger. For each substance we find that the slope of the rate-concentration function increases as a function of increasing hunger. That is, the rate of responding increases more for the high concentrations than for the low as hunger increases. These experiments employed FI schedules in which the increased rate of responding did not procure them a greater amount of food. Similarly, we found that in experiments employing choices between two concentrations where the choice is made by bar-pressing and where an FR schedule is used on each bar, the frequency of choice of the bar producing the higher concentration increases with hunger. On the other hand, we found with a brief exposure technique with no intervening instrumental response that any hunger above that experienced by *ad lib* animals results in a maximum preference for the highest concentration. This effect is apparently fairly independent of the difference in concentration between the two choices. When animals are made thirsty, they fail to discriminate between solutions differing in concentration except at the most extreme values. This failure occurs in the bar-pressing, brief exposure, and *ad lib* intake situations. Thus, our data show that when animals are hungry, they respond at higher rates and prefer the more concentrated solutions whether these solutions are nutritive or not.

We have a third line of experiments which, in part, supports your hypothesis. If the total caloric intake of *ad lib*-maintained rats offered both sucrose solutions and Purina chow concurrently and are examined continuously, we found that all concentrations except the lowest are consumed in amounts such that a fixed proportion of the total caloric intake comes from the sucrose. For adult male rats we found that at all concentrations the rat takes approximately 60% of his total

caloric intake from sucrose. In this way we think we can explain the shape of the usual single bottle preference function. Here again we see a coloric requirement determining intake in *ad lib* animals.

I would like to raise another critical point. First, we have data showing that animals 22 or 46 hours hungry, which are offered a choice between sucrose and Purina chow, prefer the chow. Here is a case in which a hungry rat prefers calories to taste, or at least does not shift his intake toward the more "tasty" item of diet. It differs from the previous cases in that the choice is between different items.

DR. JACOBS: I have followed the development of your series of studies in this area and have noted their rather consistent agreement with our model. We also have noted the tendency of satiated rats to ingest a constant proportion of their total daily intake from sugar solutions, even in cases where in addition to stock diet, two glucose solutions were available for simultaneous choice. In our experiments with *ad libitum* rats, the introduction of sugar solutions produced a compensatory decrease in stock diet intake, but this was insufficient to maintain constancy of daily caloric intake. (Jacobs, H. L. J. Comp. Physiol. Psychol. **51:** 304, 1958, and Amer. J. Physiol. **203:** 1043, 1962). Thus, although caloric requirements seemed to be the major factor in these experiments, the observed overshoot shows that taste can also contribute to total intake in *ad libitum*-fed animals.

Your observation that sucrose crystals are not as palatable as would be predicted from solution perferences is not limited to hungry animals. P. T. Young tried to extend the monotonic sugar solution preference function (36% > 18% > 9%) found in satiated rats by pairing crystalline sucrose against 36% sucrose solution. He was surprised to find the solution consistently preferred to crystals. (Young, P. T. and Green, J. T. J. Comp. Physiol. Psychol. **46:** 288, 1953). Thus, crystalline sucrose does not seem to be very palatable, and perhaps even less so than your Purina Chow in your hungry animals.

J. D. DAVIS (*University of Illinois, Chicago, Ill.*): Doctors Jacobs and Sharma have described a series of experiments which, to my mind, strongly support their interpretation that the nature of the feeding schedule of an animal determines, in part, the conditions that initiate and sustain feeding. They have argued convincingly that deprivation increases the relative importance of the sensory qualities of food and decreases the relative importance of its nutritional properties.

We are conducting a series of experiments which suggest that satiety mechanisms may also depend on the nature of the feeding schedule to which the animal is adapted. These studies, which I have carried out in collaboration with Robert L. Gallagher, Robert Ladove, and Andrew Turausky, are directed toward identifying the role that humoral factors play in the regulation of food intake.

Briefly, our experimental approach is to transfuse the blood of a pair of unanesthetized rats and, immediately following the transfusion, give each animal access to a test diet for 30 minutes. The transfusion is achieved by withdrawing 2 ml of blood via chronic intravenous cannulas from both animals simultaneously, and then injecting the blood from one animal into the other. This is repeated, 2 ml at a time, until a total of 26 ml (more than the total blood volume of either rat) has been crossed. The details of this technique are available elsewhere.[1]

In one study using this technique 16 pairs of male rats were adapted to feeding schedules; one member of each pair to a 23 and ½-hour deprivation schedule, the other to *ad libitum* feeding. The food in both cases was sweetened condensed milk. After ten days of adaptation the blood of each pair was mixed as described

above 30 minutes prior to the time the deprived animal was usually fed. Immediately following mixing both members of the pair were given access to the condensed milk.

The result, shown graphically in FIGURE 1(A), was that following transfusion the milk intake of the hungry rats was reduced to 50 percent of the amount usually drunk after a 23 and ½-hour fast. In a control study exactly the same procedure was followed except that the *ad libitum* member of the pair was deprived of food for the 24 hours immediately preceding transfusion. The result, shown in FIGURE 1B, was that the intake of the deprived animal was not reduced below that normally drunk after a 23 and ½-hour fast.

Taken together, these results suggest that with free access to food a satiety factor is present in the blood that can significantly reduce the intake of a hungry rat and that a 24-hour fast is sufficient to eliminate this factor. Does this factor play a role in terminating feeding of animals adjusted to a 23 and ½-hour deprivation schedule?

We investigated this question by mixing the blood of freshly satiated and deprived rats. Both members of the pairs were maintained on a 23 and ½-hour deprivation schedule for ten days. Thirty minutes before transfusion one mem-

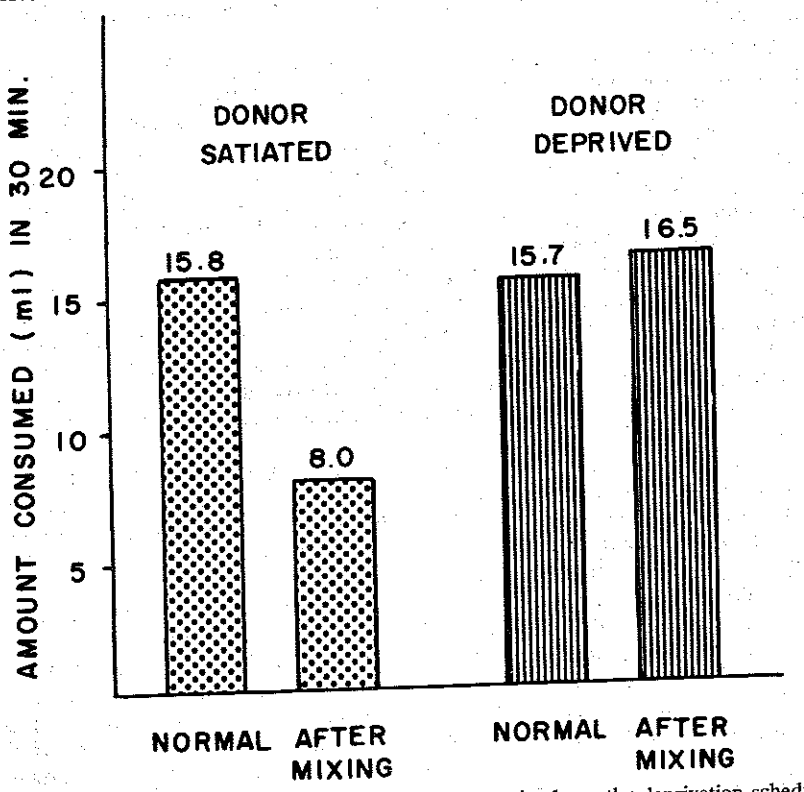

FIGURE 1. Mean intake of test diet in 30 minutes by animals on the deprivation schedule. On the left (a) the mean intake on the day prior to transfusion (normal) is compared with the mean intake of the same animals immediately following the mixing of their blood with satiated donors (after mixing). On the right (b) the same comparison is made for animals whose blood was mixed with the blood of 24-hour deprived donors.

ber of the pair was given access to condensed milk and was permitted to drink for 30 minutes. The blood of the freshly satiated animal was then mixed with that of the 23 and ½-hour hungry rat. Following mixing the intake of the hungry rats was virtually the same as that following a 23 and ½-hour fast without blood mixing (normal mean intake after a 23 and ½-hour fast = 13.7 ml; following blood mixing = 13.8 ml, N = 10).[2]

These results suggest that animals maintained on a limited feeding schedule terminate their feeding when given access to food, not because of the elevation of a humoral factor but rather, because of the accumulation of extrahumoral satiety signals (taste, gastric distention, and/or stomach chemoreception). When the animals are on *ad libitum* feeding, on the other hand, humoral satiety signals appear to be important, and feeding is perhaps terminated by the elevation of blood factors to which CNS satiety centers are responsive.

This interpretation of our results must be considered to be a tentative one since our work on the role of humoral control of feeding behavior is still in its infancy. However, the parallel we describe here between the apparent dependency of satiety mechanisms on feeding schedules and the similar dependence on feeding schedules that Doctors Jacobs and Sharma have observed of the initiating and sustaining conditions of feeding behavior is compelling. Future work on these problems may well show that the nature of the initiating, sustaining, and terminating mechanisms that operate at any given time depends in an important way on the type of feeding schedule on which the organism is maintained.

References

1. Davis, J. D. & N. E. Miller. 1966. A technique for mixing the blood of unanesthetized rats. J. Appl. Physiol. **21**: 1873–1874.
2. Davis, J. D. 1965. Food intake following blood mixing of hungry and satiated rats. Psychon. Sci. **3**: 177–178.

Dr. Jacobs: The parallel between your results and our model is of interest, suggesting that the presence of your postulated "humoral factor" may be a precondition to prime a satiety mechanism which is responsive to "caloric signals." Thus, in naturally occurring hunger, food deprivation presumably prevents the occurrence of (or deactivates?) the humoral factor, allowing the taste effect postulated in our model to modulate satiety. In our own work on cellulose dilution, gastric distention seems to be relatively unimportant, but it cannot be completely ruled out, of course.

Your data also suggest that the hungry animal *can* respond to caloric signals when primed by exogenous humoral factor, infused from a satiated donor. You might be able to use this phenomenon as an independent test of the hypothesis that hunger deactivates the humoral factor. A replication of the satiated-donor vs. hungry-recipient experiment with increasing delays between infusion and the presentation of food would be quite instructive here. In addition, it would be interesting to see if other types of hunger, e.g. induced by insulin injections, produce similar results with cross-infusion techniques.

A. J. Angyan (*New York Medical College, New York, N.Y.*): I think that Doctor Jacobs made a very important point and contributed much to our notions about the role of environmental (sensory) cues in the regulation of food and water intake by drawing a very informative feedback scheme of these regulations, which explains why and how sensory cues are made important. One question, however, often brought up in this conference – about suprasegmental and

suprahypothalamic regulation seems to need some additional explanation. As low in the phylogenetic scale as in planarians, sensory cues (e.g. taste) seem to play a very predominant role in the regulation of the animal's behavior and, paradoxically enough, this prevails in regenerating animals (cranial regenerates after section in the upper half) particularly during the period when, due to lack of the digestive tract, feeding is rendered impossible. Direct taste cues and sensory-conditioned (olfactory, chemotropic and visual) signals override even the innate negative phototropism of the animal. Discriminative orientation towards preferred food and chemicals prevails in the cranial nervous organization over all other functions, and has a tendency towards hunting (positive feedback) until such time when the tail end grows out and food consumption and digestion become possible. We interpreted this braking role of the caudad neural organizations as a negative feedback effect upon the predominantly orienting and sensory-conditioning of head regenerates performed by the integrated neural organizations which operate in clear-cut division of systems of antagonistic excitatory and inhibitory balance and thus, can keep the effects of learning and conditioning within a homeostatic framework even in these lower animals. These observations (Angyan & Nemeth, 1957, published only in part)[1] seem to indicate that, at least for us, Dr. Jacobs's seemingly paradoxical scheme reflects perhaps a more general logical plan of organization of behavior than one applicable only to food and water intake.

On a higher developmental level, in dogs with similar training for Pavlovian salivary-conditioned responses for food reward, we found (1954)[2] that in the initial period of training before a discriminative equilibrium for sensory food cues has been established and orienting, alert activity prevails, conditioned salivary responses can be developed in previously overfed animals as well as in hungry ones. However, when a stable system for sensory food cues has been developed in the course of a lengthy training, *ad libitum* pre-experimental overfeeding brings about a swiftly developing inversion and subsequent inhibition of the conditioned salivary responses, together with a tendency to sleep in the experimental setting. Interestingly enough, small doses of insulin, without influencing blood glucose levels, affected an immediate arousal of these inhibited animals in response to positive (reinforced) sensory cues (conditioned signals) and a marked but short feeding response after which the animals went back to sleep, which they maintained during stimulation with negative (inhibitory unreinforced) sensory signals. (Angyan & Lissak, 1954; Angyan, 1956 & 1957).[3,4]

It seems to be clear both from the contributions of the very interesting work of the Kanazawa group as well as from the work of Sterman *et al.* and Morgane reported at this conference that there is some "lawful correlation" between food and water intake and the central corticopetal and corticofugal systems regulating sleep and wakefullness at the brain stem and cortical levels. Thus, they should be perhaps at least tentatively included in any feedback model of the regulation of food and water intake. The question might be raised that, on the basis of such a perfected model, experiments dealing with the importance of hypothalamic regulation in food and water intake have to be re-evaluated by a parallel assessment of the higher sensory-regulating functions in a more comprehensive scheme.

References

1. ANGYAN, A. V. & G. NEMETH. 1957. Investigations on unconditioned and conditioned adaptation mechanisms of fresh and sea water flatworms (tubellaria) before and after regeneration. Acta Physiol. Hung. suppl.

2. ANGYAN, A. V. & K. LISSAK. 1954. Relationship of conditioned and unconditioned reflex excitabilities of salivary conditioned reflexes as influenced by previous feeding and insulin treatment. Acta Physiol. Hung. 6: 2–3, 289–299.
3. ANGYAN, A. V. 1956. Periodic changes of cortical electric activity patterns during salivary-conditioned reflex stereotype of dogs. Acta Physiol. Hung. 1: 19–32.
4. ANGYAN, A. V. An attempt for a comparative analytico-typological investigation of human and animal conditioned reflex behavior with structural inferences upon underlying nervous organization. Thesis of the 1st World Congress of Neurological Sciences. Brussels, July 27, 1957.

DR. JACOBS: In the stage of development of the model we presented here, we have limited our interest to food intake, and to mammalian species, and have not attempted to incorporate hypotheses about the important issues raised by Dr. Angyan. These issues will have to be taken into account as we begin to understand the mechanisms operating in systems of this type. Thus, any attempts to relate specifically the two suggestive examples presented by Dr. Angyan to our model would be premature. I will add one comment, however, to his suggestion that the hypothalamic systems mediating food intake are integrally related to the reticular, thalamic, and cortical systems regulating sleep and wakefullness. Dr. Chester Pearlman (personal communication) has recently pointed out to me that informal observations on both cat and man deprived of paradoxical sleep ("dream" deprivation experiments) suggest increases in hunger drive and food-associated activity. Since these experiments can readily be performed on man and animals, they may provide a method to analyze the "lawful correlation" between the systems regulating intake and level of awareness and arousal.